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34

VCM

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In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

P, 24,550

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

eue-H02995-34-p024550

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal [illegible]ion is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with [illegible] or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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Predictable control of stress responses from induction through recovery

***REDUCES** stress response to intubation and surgical stimulation*[1,2]

***PROVIDES** intraoperative hemodynamic stability*

***CONTROL** of the stress response is associated with less postoperative morbidity*[3,4]

***MAINTAINS** postoperative analgesia with faster recovery of respiratory drive*[5]

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.
DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.
INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.
CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.
Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.
Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.
ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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Anesthesia
and Analgesia

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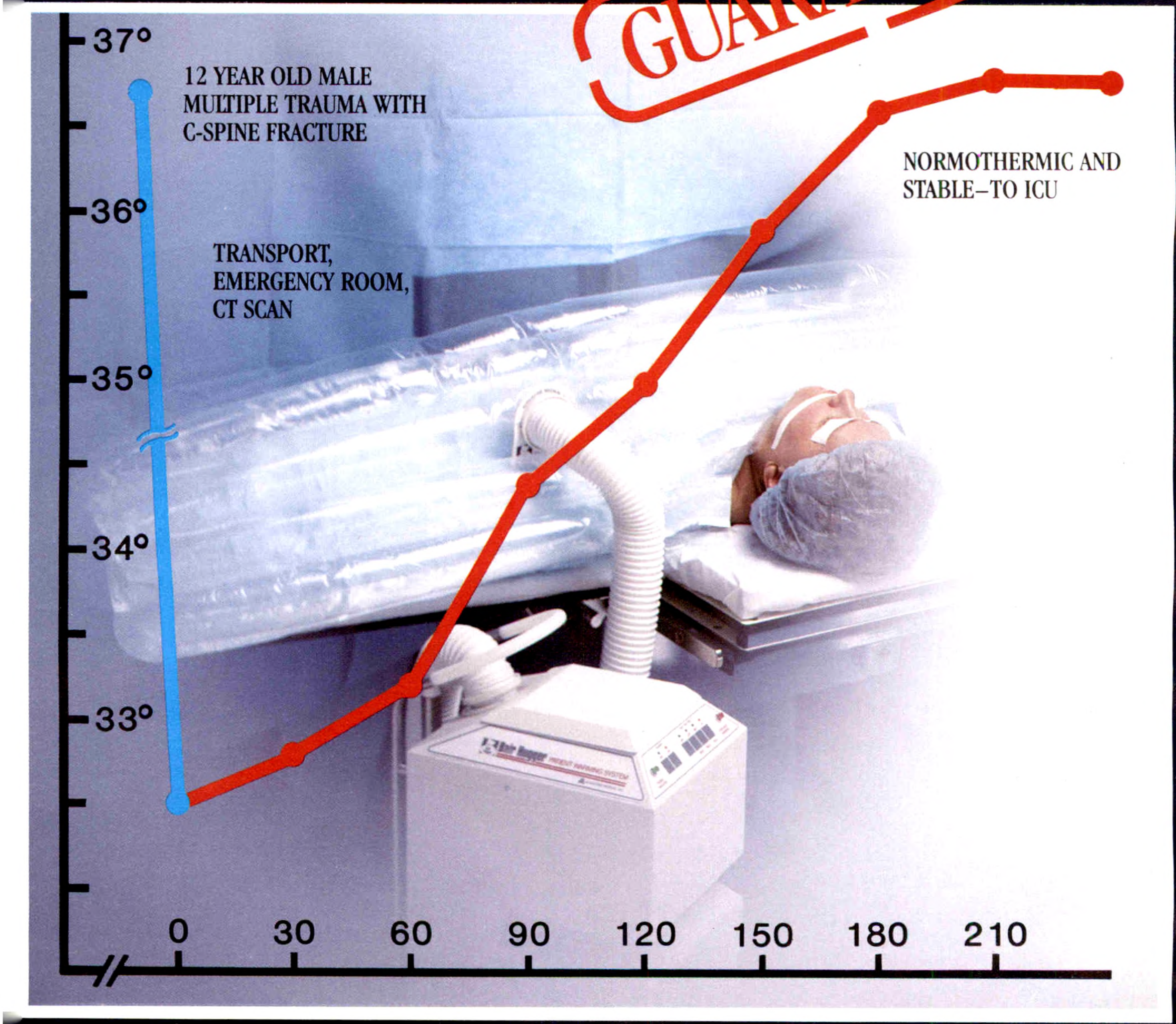

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*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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March 1987, April 1988
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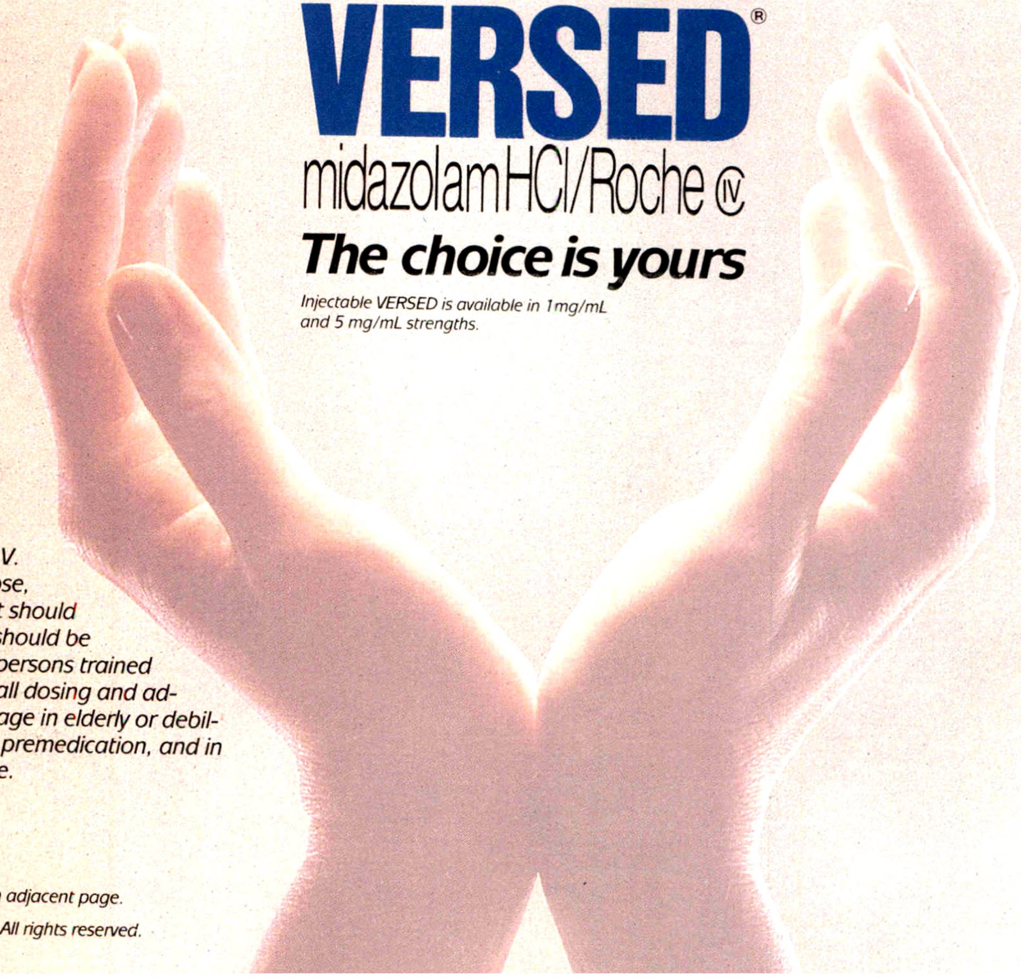

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References: 1. White PF. *Anesthesiology.* 1982;57:279-284. **2.** Roche Scientific Summary. The Evaluation of VERSED® (brand of midazolam HCl/Roche) CIV, Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, New Jersey, 1986.

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>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1mg/mL formulation or dilution of the 1mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period.

Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication,

particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses. Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0988

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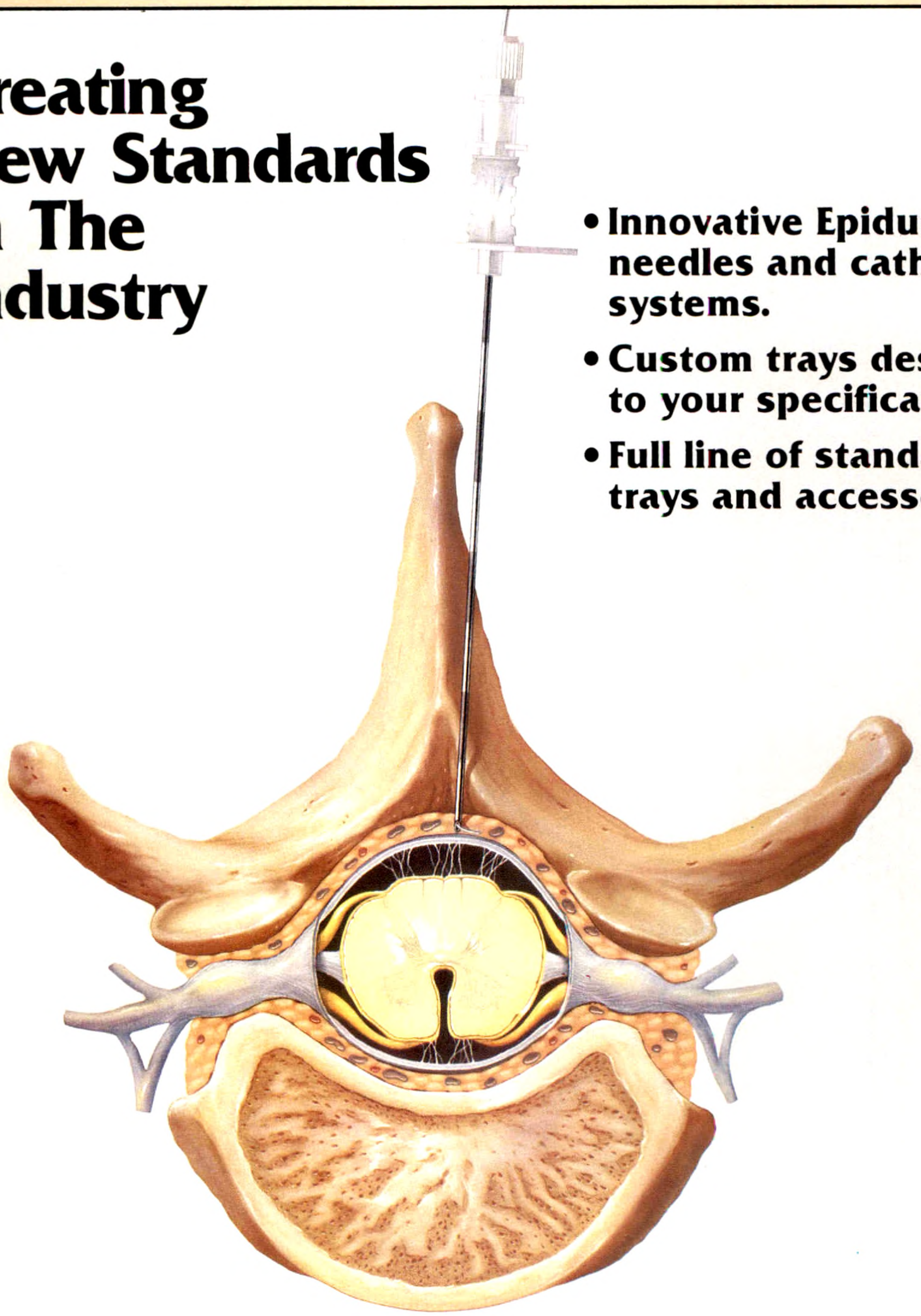

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

IARS 65TH CONGRESS

Friday, March 8 through Tuesday, March 12, 1991
Marriott Rivercenter, San Antonio, Texas

CALL FOR PAPERS

AUGUST 3, 1990, DEADLINE

The Program Committee for the IARS 65th Congress cordially invites submission of abstracts for consideration as oral or poster presentations at the 1991 meeting in San Antonio. The official abstract application and transmittal forms are available from the Cleveland office of the IARS:

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, OH 44122, USA
Telephone: (216) 295-1124

Please note the absolute deadline for receipt of completed applications is August 3, 1990. Please request forms promptly—either by calling the telephone number above or returning the form below.

Noel W. Lawson, MD, Chairman
65th Congress Program Committee

- -

International Anesthesia Research Society
3645 Warrensville Center Rd.
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Please send ______ abstract submission packet(s) for the IARS 65th Congress to:

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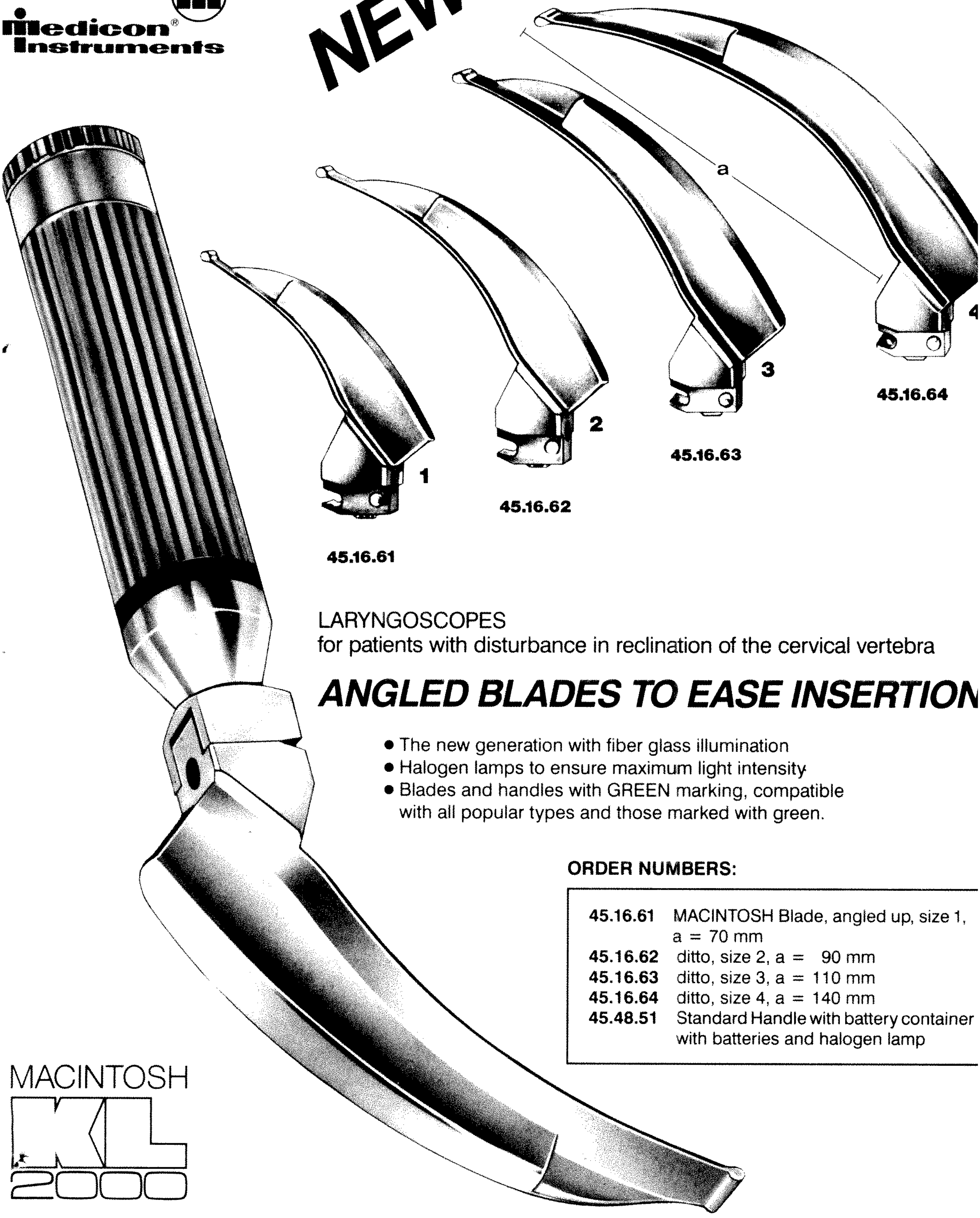

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HE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1990 AWARDS

At the IARS 64th Congress in March 1990, the Board of Trustees announced recipients of the 1990 Award as follows:

Brian G. Bertha, MD, Mayo Clinic, Rochester, MN:
"Do Inotropic and Vasopressor Drugs Stimulate or Attenuate Platelet Aggregation and Thrombosis in Pig Coronary Arteries?"

Karen B. Domino, MD, University of Washington Harborview Medical Center, Seattle, WA:
"Effect of Changes in PCO_2 *on the Matching of Ventilation and Perfusion in Normal and Edematous Lungs"*

Roderic G. Eckenhoff, MD, University of Pennsylvania Medical Center, Philadelphia, PA:
"Subcellular Distribution of Inhalational Anesthetics"

Robert Allen Pearce, MD, PhD, University of Wisconsin, Madison, WI:
"Effect of Volatile Anesthetics on Neuronal Inhibition in the Rat Hippocampus In Vitro"

Christoph Stein, MD, Ludwig-Maximilians-Universitat, Munich, West Germany:
"Peripheral Opioid Receptors Mediating Antinociception in Inflammation: Endogenous Ligands"

David O. Warner, MD, Mayo Clinic and Mayo Foundation, Rochester, MN:
"Volatile Anesthetics and Epithelium-Mediated Relaxation in Airway Smooth Muscle"

1991 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1991 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 14, 1990. Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1991 Award(s) will be announced at the Annual Scientific Meeting (65th Congress) of the International Anesthesia Research Society to be held at the Marriott Rivercenter, San Antonio, Texas, March 8–12, 1991.

NEW
FROM SYNTEX LABORATORIES

THE FIRST
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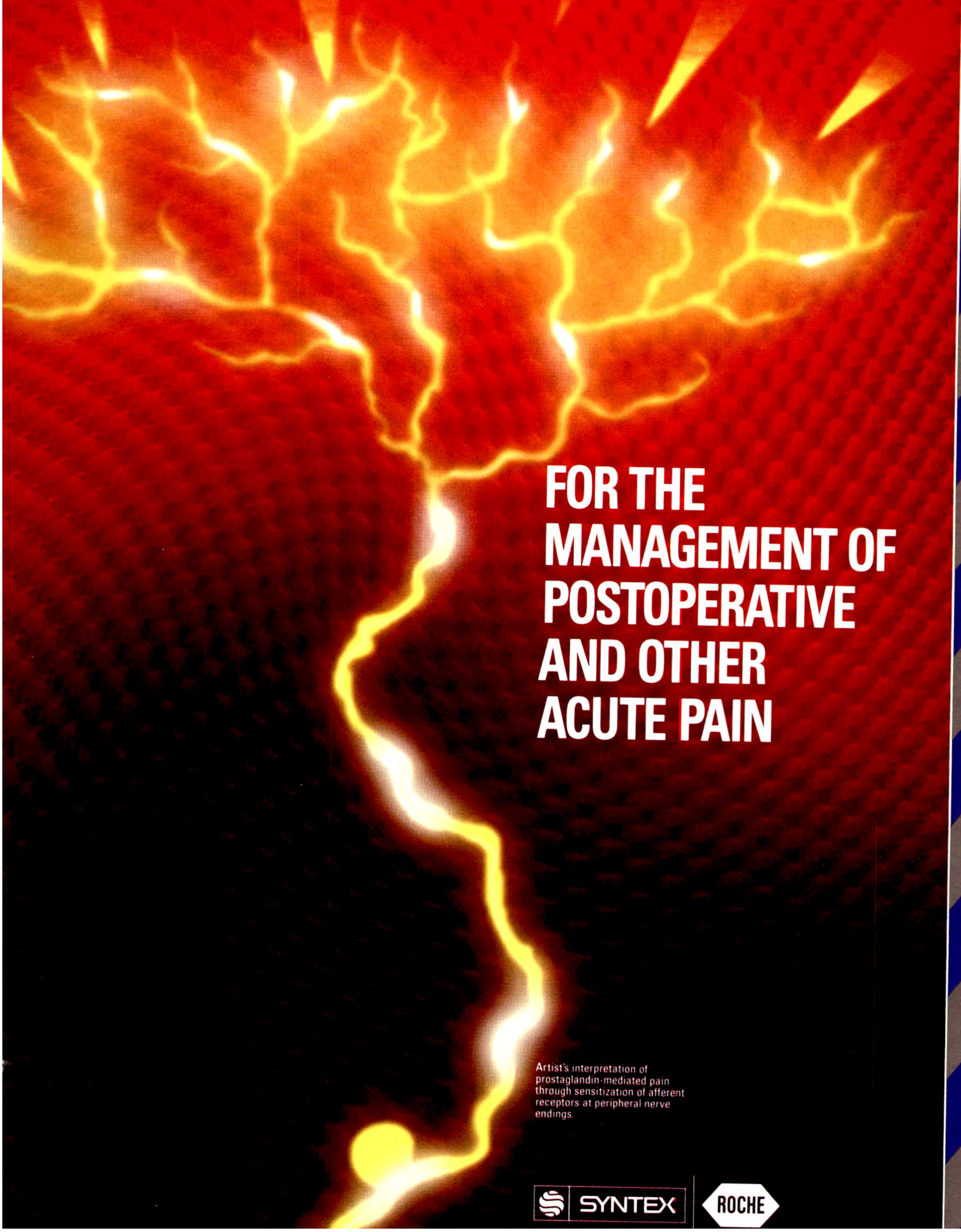
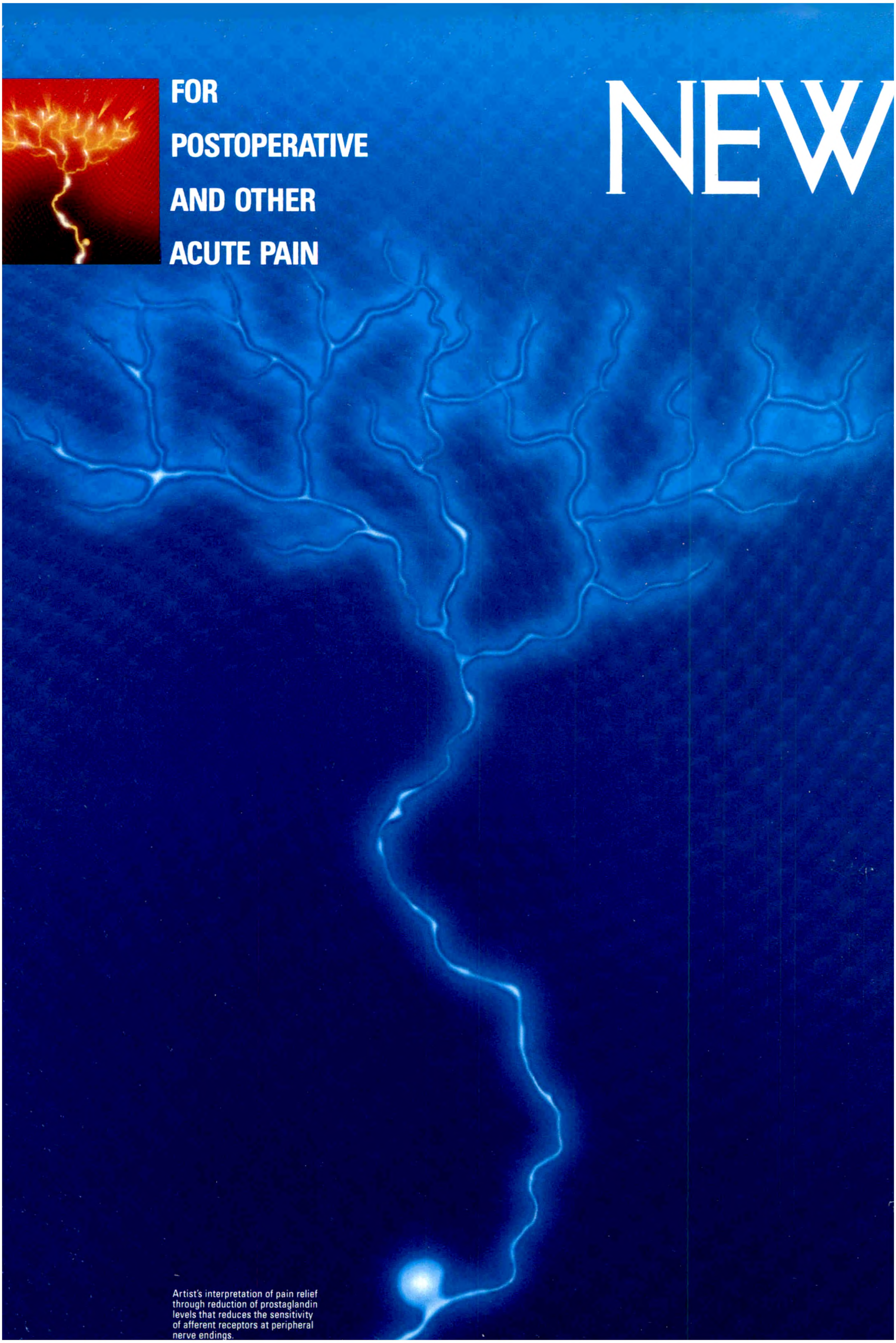


FOR THE
MANAGEMENT OF
POSTOPERATIVE
AND OTHER
ACUTE PAIN

Artist's interpretation of prostaglandin-mediated pain through sensitization of afferent receptors at peripheral nerve endings.

SYNTEX ROCHE



Artist's interpretation of pain relief through reduction of prostaglandin levels that reduces the sensitivity of afferent receptors at peripheral nerve endings.

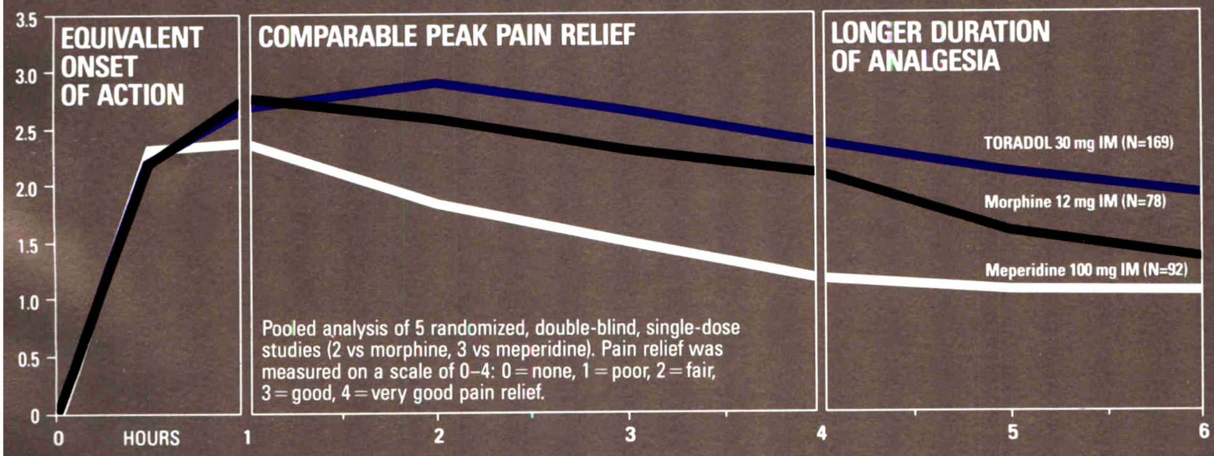
TORADOL® IM INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

The first peripherally acting analgesic with efficacy comparable to morphine 12 mg and meperidine 100 mg

Analgesic efficacy of TORADOL IM administered 24–72 hours postsurgery[1]



Pooled analysis of 5 randomized, double-blind, single-dose studies (2 vs morphine, 3 vs meperidine). Pain relief was measured on a scale of 0–4: 0 = none, 1 = poor, 2 = fair, 3 = good, 4 = very good pain relief.

Documented efficacy following a broad range of surgical procedures:

General, orthopaedic, gynecologic (not for obstetric use)

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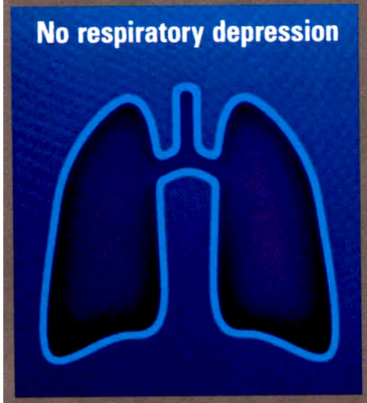
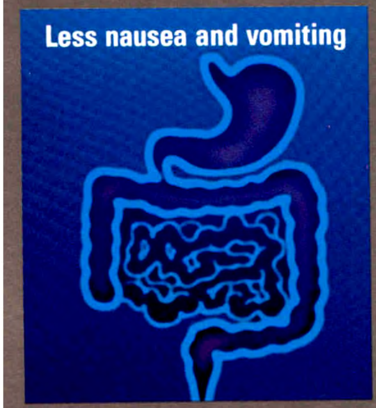
*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings" and "Precautions" sections of prescribing information.

[1] Data on file, Syntex Laboratories, Inc., Document #90037-1.

Please see brief summary of prescribing information on last page of this advertisement.

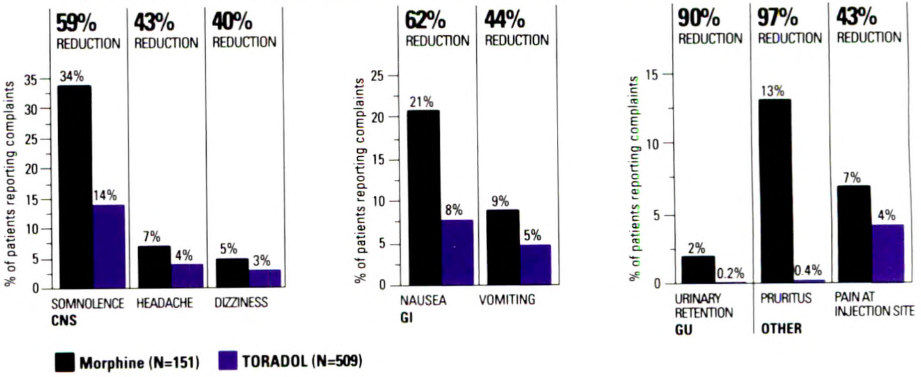




START RECUPERATION WITHOUT NARCOTIC SIDE EFFECTS[1]*

- 62% less nausea and 44% less vomiting
- 48% fewer CNS side effects
- No respiratory depression
- No hypotension
- 1-day earlier resumption of normal bowel function following major abdominal surgery
- No difference in clinically significant postoperative bleeding with TORADOL IM (0.4%) as compared to opiates (0.2%)

Comparison of most frequently reported side effects in 2 multi-dose studies (TORADOL IM vs morphine)**



Adverse reactions rates from short-term use of NSAIDs are generally from 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL IM.

FOR
POSTOPERATIVE
AND OTHER
ACUTE PAIN

NEW

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*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings," "Precautions," and "Adverse Reactions" sections of prescribing information.

**Most frequently reported side effects in major body systems with the exception of the cardiovascular system. 2% of patients treated with Toradol reported vasodilation as compared to 1% of patients treated with morphine.

1. Documented in 2 randomized, double-blind, multi-dose studies in which 509 patients received ketorolac 30 mg and 151 patients received morphine 10 mg or morphine 12 mg. Bowel function was evaluated in a subset of 47 patients undergoing gastric bypass surgery. Data on file, Syntex Laboratories, Inc., Document #90037-2.
2. Data on file, Syntex Laboratories, Inc., Document #90037-3.

Please see brief summary of prescribing information on last page of this advertisement.

Analgesic therapy well suited for postoperative use

TORADOL IM is not an opiate

- Does not act on opiate receptor sites
- No potential for abuse
- No special restrictions or controls required

May be an appropriate alternative to narcotics for:

- Patients with narcotic allergy or intolerance
- Patients with a history of, or potential for, drug abuse or dependence

Special advantages may facilitate postoperative recuperation

- Patients with COPD or the obese–no negative effects on pulmonary function
- Ambulatory surgery patients–less CNS impairment (e.g., 59% less somnolence and 40% less dizziness)

Optimize analgesia on the day of surgery

- On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing
- On average, only one supplemental dose of narcotics may be required[2]

TORADOL® IM
INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

P 24,550

FOR
POSTOPERATIVE
AND OTHER
ACUTE PAIN

NEW
TORADOL® IN
INJEC

(KETOROLAC TROMETHAMINE) 15,
60

OPTIMIZE ANALGESIC THERAPY FOR THE POSTOPERATIVE PATIENT

PROPER DOSAGE POSTOPERATIVELY

For maximum analgesia:

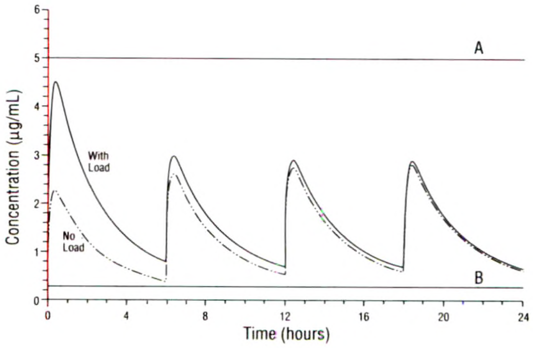
- Give patients prompt pain relief: start with loading dose of 60 mg IM
- Follow with maintenance dose of 30 mg IM Q6h to control pain
- The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter*

Simulated incremental plasma concentrations after 2 multi-dose regimens: (1) TORADOL $^{\mathrm{IM}}$ 30 mg Q6h (no load); (2) TORADOL $^{\mathrm{IM}}$ 60 mg LOADING DOSE followed by 30 mg Q6h

A = Plasma concentration above which side effects are more frequent

B = Estimated concentration required to obtain 50% decreases in pain intensity scores in dental surgery pain

Achieve optimal peak and trough plasma levels by starting with a loading dose (e.g., 60 mg), while maintaining plasma levels within the recommended therapeutic range. Follow with maintenance doses (e.g., 30 mg every 6 hours) to keep plasma levels in the optimal range.



Patient Selection: Use in patients with moderate-to-severe postoperative pain following general, orthopaedic, or gynecologic surgery (not for obstetric use)

Lower doses:

- Recommended for patients under 50 kg (110 pounds), patients over 65 years of age, and patients with reduced renal function
- Start with loading dose of 30 mg IM
- Follow with maintenance dose of 15 mg IM Q6h to control pain

On the day of surgery, some TORADOL $^{\mathrm{IM}}$ patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing (not compatible in same syringe)

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*Dosages above those recommended are not associated with commensurate increases in efficacy.

Please see brief summary of prescribing information on last page of this advertisement.

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SYNTEX

First Symposium of the

International Society for Perioperative Care in Liver Transplantation

September 7 & 8, 1990

V*ista International Hotel*
Pittsburgh, Pennsylvania, U.S.A.

This two-day program will encompass all aspects of care in liver transplantation through presentations and scientific papers on recent developments, controversial issues, and current research activities.

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ADVANCES
IN PAIN
MANAGEMENT
UPDATE 1990

September 14 - 16, 1990
Houston, Texas

Management of pain has become an important issue in health care today. Clinicians and communities are not aware of the advances in pain medicine. The lectures will include discussion on acute, chronic and cancer pain. The participants should be able to understand the basic mechanisms of pain syndromes, the rationale for management and efficacy of various modalities of treatment. In addition to lectures, there will be small groups of "in-depth" teaching workshops emphasizing the various aspects of acute pain and offer tips on practical management of pain patients. The faculty includes distinguished experts from around the world. **Registration is limited, so register early!**

COURSE DIRECTORS: *P. Prithvi Raj, M.D.*, Professor of Anesthesiology, The University of Texas Medical School at Houston; Director, The University Center for Pain Medicine at Hermann. *C. Stratton Hill, Jr., M.D.*, Director, Pain Center, the University of Texas M.D. Anderson Cancer Center, Houston,Texas.

FOR MORE INFORMATION, CALL
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TORADOL® IM (ketorolac tromethamine)

Brief Summary
TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 μg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 μg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels, hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the in vivo mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery. **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. **Pediatric Use:** TORADOL is not recommended for use in children. **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. **Incidence greater than 1%:** Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%-9%. Reactions occurring in less than 3% are unmarked. **Incidence 1% or less:** Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. In vitro, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses >100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others

Mfd. for Syntex Laboratories, Inc.
Palo Alto, CA 94304
by Survival Technology, Inc.
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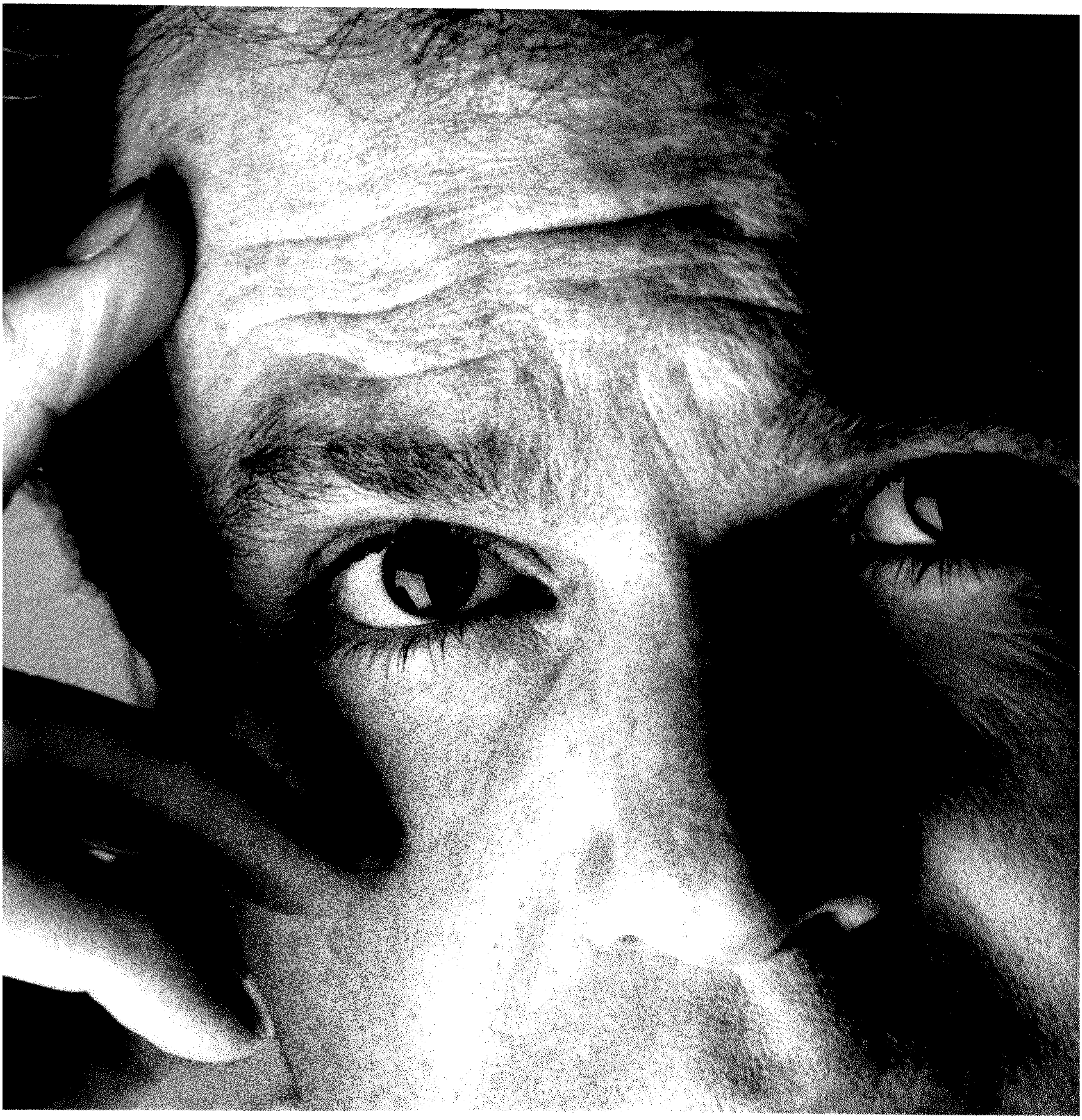
SYNTEX

02-2434-40-00 December 1989

"Doctor, I need to know. Is there any way you can avoid giving me blood products?"



In plasma volume expansion

YES!

Hespan®

(hetastarch)

Derived from corn, not blood…no risk of serum-transmitted diseases with HESPAN®

HESPAN® is derived from a waxy starch consisting almost entirely of amylopectin.[1] Consequently, there is no risk of serum-transmitted diseases, such as AIDS or hepatitis, with HESPAN®.[2] Furthermore, HESPAN® is as effective as albumin for plasma volume expansion.[2,3]

Flexible plastic bag won't shatter and permits rapid pressurized infusion

HESPAN® is packaged in a lightweight plastic bag. The compact, unbreakable bag can be stored easily, retrieved quickly, and is designed for rapid setup and infusion.

For more information about HESPAN®, please call **1-800-527-2601.**

Please see brief summary of prescribing information on the following page.

NDC 0094-0037-44
HESPAN
500 mL
6% hetastarch
0.9% sodium chloride injection
LOT
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EXP
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Additive Port
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References: 1. Hespan® Prescribing Information. **2.** Waters LM. Christensen MA, Sato RM: Hetastarch: An alternative colloid in burn shock management. *J Burn Care Rehabil* 1989;10:11–16. **3.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983;11:839–850.

Hespan® (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

Brief Summary of Prescribing Information

CONTRAINDICATIONS

HESPAN is contraindicated in patients with known hypersensitivity to hydroxyethyl starch, or with bleeding disorders, or with congestive heart failure where volume overload is a potential problem. HESPAN should not be used in renal disease with oliguria or anuria not related to hypovolemia.

WARNINGS

Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of HESPAN. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count, hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/mL (normal 0.0–7.0 mg/mL) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS

The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing) bleeding due to hemodilution (see Warnings), and circulatory overload and pulmonary edema (see Precautions).

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion: HESPAN is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred.

Dosage in Leukapheresis

250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The safety and compatibility of other additives have not been established.

HOW SUPPLIED

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

HESPAN is supplied sterile and nonpyrogenic in 500 mL intravenous plastic infusion containers (NDC 0056-0037-44) and 500 mL intravenous glass bottles (NDC 0056-0037-05).

CAUTION

Federal (USA) law prohibits dispensing without prescription.

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Revised: April, 1989

H-24753

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In recent advertising, a medical equipment remarketer has stated that Ohmeda will fully service anesthesia machines which have been refurbished by their organization. Additionally, they state that such service will be conducted in the purchaser's facility.

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ANESTH ANALG
1990;70:577–82

Cardiovascular Effects and Regional Clearances of Intravenous Ropivacaine in Sheep

Albert J. Rutten, BSc, Laurence E. Mather, PhD, FFARACS, Craig Nancarrow, FFARACS, PhD, Paul A. Sloan, MD, FRCP(C), and Colin F. McLean, Dip Chem

RUTTEN AJ, MATHER LE, NANCARROW C, SLOAN PA, McLEAN CF. Cardiovascular effects and regional clearances of intravenous ropivacaine in sheep. Anesth Analg 1990;70:577–82.

The purpose of this study was to determine the cardiovascular effects and the total body and regional clearances of ropivacaine during its continuous intravenous infusion to subtoxic levels in five conscious unrestrained sheep that had been previously prepared with appropriate intravascular cannulas. Ropivacaine HCl·H_2O, 1 mg/min, produced constant arterial blood concentrations which ranged from 0.70 to 1.84 mg/L. This caused no appreciable cardiovascular effects. The mean total body clearance (±SD) of ropivacaine was 1.00 ± 0.27 L/min. There was significant clearance of ropivacaine by the liver (0.85 ± 0.32 L/min), gut (0.09 ± 0.07 L/min), and kidneys (0.04 ± 0.03 L/min). There was no significant clearance of ropivacaine by the lungs, brain, heart, or hindquarters. It was concluded that the liver accounts for the majority of ropivacaine clearance.

Key Words: ANESTHETICS, LOCAL—ropivacaine. PHARMACOKINETICS, ROPIVACAINE.

Ropivacaine hydrochloride monohydrate (hereafter referred to as ropivacaine), the *N*-*n*-propyl homologue of bupivacaine, is currently undergoing investigation for possible clinical use (1). Unlike bupivacaine, which is prepared and used as a racemic mixture (2), ropivacaine is prepared as the single enantiomer, *S*-(-)-1-propyl-2',6'pipecoloxylidide hydrochloride monohydrate. Studies of its local anesthetic activity in different species indicate that ropivacaine is an effective local anesthetic agent. Compared to bupivacaine, ropivacaine is longer acting upon infiltration, is equally effective in peripheral (sciatic) nerve blocks, and has a slightly shorter duration of action in spinal and epidural anesthesia (1,3).

Comparative pharmacokinetic studies in dogs and humans have indicated that after intravenous (IV) infusion the mean total body clearance (TBCl) of ropivacaine is slightly greater than that of bupivacaine, and that after epidural administration the pharmacokinetic profiles of the agents are similar (4–7). It has recently been recognized that the TBCl of drugs, including amide local anesthetics, may not be measured correctly using conventional pharmacokinetic techniques because a component of distribution may be erroneously included in the measured clearance (8). Although the mean TBCl is useful for comparative studies, it does not define the regions of drug clearance and therefore does not allow insightful analysis of the regional drug kinetics when cardiovascular or other physiologic changes may occur coincidently or as a response to the drug being studied (9).

The aim of this study was to determine the cardiovascular effects and the total body and regional clearances of ropivacaine during its continuous IV infusion to subtoxic levels in conscious unrestrained sheep.

Methods

Approval was given by the institutional ethics review committee for this study to be performed. One study was performed in each of five sheep (mean weight 49 ± 8 kg) previously prepared with chronic intravascular catheters to enable drug infusion, cardiovascu-

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lar monitoring, and regional blood sampling for blood flow indicator and ropivacaine analyses. Each animal received a two-stage IV infusion of ropivacaine to produce constant arterial blood drug concentrations. Another four sheep each received a single dose of ropivacaine as an IV bolus to determine the fraction of dose excreted into the urine.

Animal Preparation

The general methods and materials used for animal preparation have been described in detail in previous publications from this laboratory (10–12); the methods specific to the present study are briefly described here. Under general anesthesia, a left-sided thoracotomy was performed to ligate the hemiazygos vein, which, in the sheep, contributes systemic venous blood to the coronary sinus. Intraabdominal catheters were placed directly into the abdominal aorta (distal to the renal artery and proximal to the iliac bifurcation) and mesenteric and portal veins via left paravertebral and right subcostal skin incisions, respectively. After surgical exposure of the vessels in the neck, two arterial catheters were placed in the right carotid artery with their tips positioned approximately 2 cm above the aortic valve. Catheters were placed in the right jugular vein with their tips in the coronary sinus, left renal vein, posterior vena cava (PVC), right hepatic vein, and right atrium (two catheters) and a flow-directed thermodilution catheter was placed with its tip in the pulmonary artery. An additional catheter was placed in the sagittal sinus via a frontal incision and a trephine hole in the parietal bone.

At least 1 wk was allowed for the sheep to recover from surgery before the study was performed.

Baseline Cardiovascular and Blood Flow Measurements

Mean arterial pressure (MAP) was determined using an aneroid gauge connected via an extension line to one of the arterial catheters. Heart rate (HR) was determined at the same time as MAP from the oscillation rate of a small bubble introduced into the extension line. Cardiac output was determined using the pulmonary artery thermodilution catheter after ice-cold saline injection (10 mL) into a right atrial catheter.

Gut and hindquarter blood flows were each measured by indicator dilution using infusion into the mesenteric vein and abdominal aorta of the indicators sodium para-aminohippurate (PAH) and sodium bromosulfophthalein (BSP), respectively. Liver and kidney blood flows were each measured at times similar to those for gut and hindquarter blood flow determinations by the Fick method using BSP and PAH, respectively. Steady-state blood concentrations of the indicators were achieved with two-stage infusions using a constant-rate two-channel infusion pump (model 940, Harvard Apparatus, Millis, Mass.) with calibrated glass syringes: a 15-min loading dose of BSP and PAH (32 and 8 mg/min, respectively) was followed by a maintenance infusion (16 and 4 mg/min, respectively). After 45 min of maintenance infusion, simultaneous ascending aortic and appropriate regional venous blood sample sets (0.4 mL) were drawn at 10-min intervals for a further 40 min. At the same times, MAP, HR, arterial pH, and blood-gas tension measurements were obtained simultaneously. These were termed "baseline" measurements.

Gut and hindquarter blood flows were calculated from the quotients of the PAH and BSP maintenance dose rates, respectively, and from the appropriate venous-arterial concentration differences at steady state. Liver and kidney blood flows were calculated from the quotients of the BSP and PAH maintenance dose rates, respectively, and from the appropriate regional arterial-venous concentration differences at steady state.

Ropivacaine Administration

After baseline cardiovascular and regional blood flow measurements were made, constant blood ropivacaine concentrations were achieved with a two-stage infusion of ropivacaine into a right atrial catheter. Loading doses of 3 mg/min for 10–20 min were followed immediately by maintenance doses of 1 mg/min to 240 min. This produced blood ropivacaine concentrations that encompassed the range observed by others in epidural clinical trials (6,7).

The last 60 min of maintenance infusion was regarded as the "steady-state" period. During this period, simultaneous blood samples (0.5 mL, individually weighed) were obtained at 15-min intervals from the aortic, pulmonary artery, sagittal sinus, coronary sinus, hepatic, portal, renal, and PVC catheters for the determination of blood ropivacaine concentrations. During the steady-state period MAP, HR, arterial pH, and blood-gas tensions were determined, together with cardiac output and liver, kidney, gut, and hindquarter blood flows by the methods described above.

Pharmacokinetic Analysis

The TBCl of ropivacaine was obtained from the ratio of the maintenance infusion rate to mean arterial blood ropivacaine concentration during the steady-state period. The regional clearances of ropivacaine were determined from the relevant products of the regional extraction ratios and regional blood flows. The indicator dilution measurement of gut blood flow was considered to be unreliable due to apparent streaming of the PAH. It was therefore taken as 80% of liver blood flow (10,13), and the splanchnic component of hepatosplanchnic clearance was estimated from the product of the arterial-portal venous ropivacaine extraction ratio and the estimated gut blood flow.

Ropivacaine Concentrations

Ropivacaine concentrations in blood and urine were determined by gas-liquid chromatography with nitrogen selective detection after solvent extraction using methods previously described for lidocaine and bupivacaine (12).

Statistical Analysis

For each experiment, differences in mean values during ropivacaine infusion from baseline in MAP, HR, arterial pH, and blood-gas tensions, and blood flow measurements, were compared using Student's t-test for paired data. Individual regional extraction ratios and clearances were examined by the one sample t-test to determine whether they were significantly different from zero. For all tests, $P < 0.05$ was considered to be statistically significant.

Results

Cardiovascular and Blood Flow Measurements

Mean values of MAP, HR, arterial pH, and blood-gas tensions during baseline and ropivacaine treatment periods for each experiment are presented in Figure 1, and the relevant blood flow measurements during these periods are shown in Figure 2.

With the exception of kidney blood flow (P = 0.04), administration of ropivacaine did not affect the other cardiovascular parameters (Figures 1 and 2).

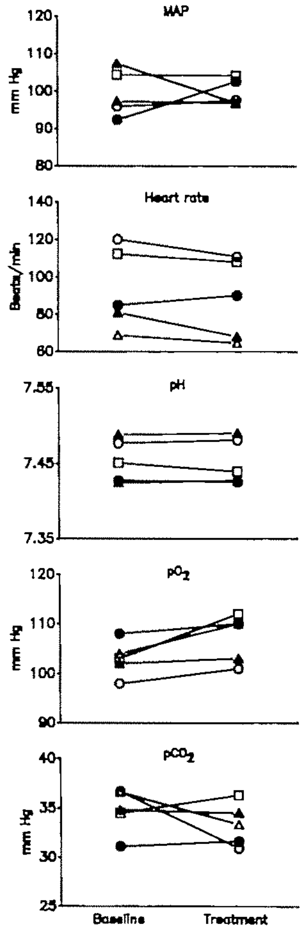

Figure 1. Comparison of mean arterial pressure (MAP), heart rat
arterial blood pH and gas tensions before (baseline) and during t
fourth hour of ropivacaine infusion. Values shown are the mea
of each period. No significant differences in the respective valu
($P > 0.05$) were detected between the two periods. ○, sheep 1; ●
sheep 2; △, sheep 3; ▲, sheep 4; □, sheep 5.

Ropivacaine Kinetics

The resultant arterial blood ropivacaine concentr
tions for each animal are shown in Figure 3: consta
blood concentrations occurred in four of the fiv
animals after about 2–3 h. In one animal (sheep 3
there was a slow increase in arterial blood ropivacain
concentration throughout the study period; subs
quent determinations of extraction ratios and clea
ances were based on the last set of concentratio
values (240 min).

With the exception of the liver, the arteria
regional venous concentration gradients were smal
The regional extraction ratios of ropivacaine are pr
sented in Figure 4. During the steady-state perio
ropivacaine was extracted significantly by the liv
(0.53 ± 0.20) and, to a small extent, by the gut (0.07
0.05) and kidneys (0.04 ± 0.03), but not by the lung
brain, or hindquarters. The corresponding region
clearances were liver (0.85 ± 0.32 L/min), gut (0.09

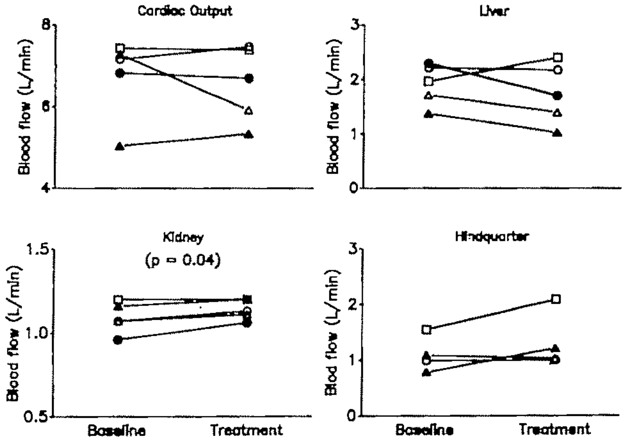

Figure 2. Comparison of cardiac output, liver, kidney, and hindquarter blood flow before (baseline) and during the fourth hour of ropivacaine infusion. Values shown are the means for each period. With the exception of kidney blood flow ($P = 0.04$) there were no significant differences in the respective values between the two periods. ○, sheep 1; ●, sheep 2; △, sheep 3; ▲, sheep 4; □, sheep 5. Hindquarter blood flow was not measured in sheep 2.

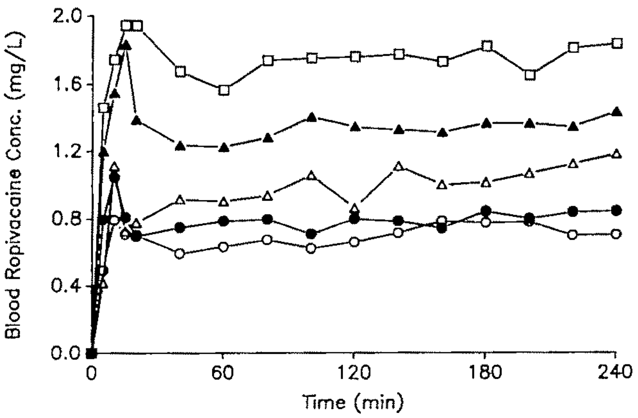

Figure 3. Arterial blood ropivacaine concentrations during the infusion period. ○, sheep 1; ●, sheep 2; △, sheep 3; ▲, sheep 4; □, sheep 5.

0.07 L/min), and kidneys (0.04 ± 0.03 L/min). Clearances of ropivacaine by these organs as well as TBCl are shown in Figure 5. Analysis of urine showed that negligible quantities of ropivacaine were excreted unmetabolized (0.06% ± 0.03% of the dose) and confirmed that the kidneys were a minor site for elimination of ropivacaine.

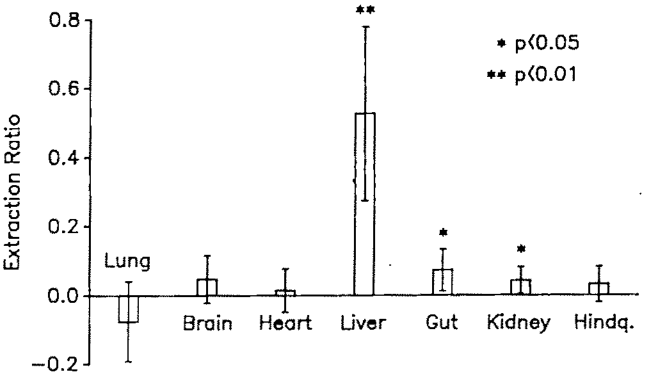

Figure 4. Regional extraction ratios during the fourth hour of ropivacaine infusion. There was significant extraction of drug by the liver ($P < 0.01$), gut ($P < 0.05$), and kidney ($P < 0.05$), but not for lung, brain, heart, and hindquarters (hindq.). Values shown are the population means ±95% confidence interval.

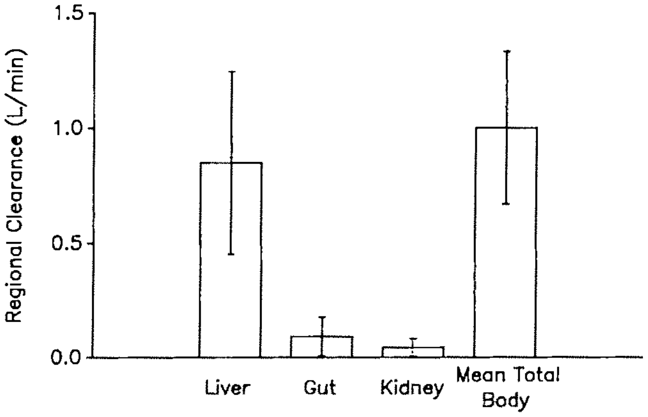

Figure 5. The relationship of relevant regional clearances to the mean total body clearance of ropivacaine (calculated from the ratio of the maintenance dose rate divided by arterial blood drug concentration at steady state). Gut regional clearance was derived using an estimated blood flow of 80% of total hepatic flow. Values shown are the population means ±95% confidence interval.

Discussion

Intravenous infusion of ropivacaine at 1 mg/min produced constant arterial blood concentrations that ranged from 0.70 to 1.84 mg/L. These concentrations produced no notable effects on the cardiovascular variables measured. The slight increase in kidney blood flow (0.05 ± 0.04 L/min) was not considered to have relevance. This provides corroboration for the report that the IV bolus administration of ropivacaine producing maximum blood drug concentrations ranging from 1.56 to 3.07 mg/L in dogs had no effect on blood pressure and HR (4).

Extensive lung tissue uptake of bupivacaine, etidocaine, and lidocaine has been shown to occur in vitro (14), and there is evidence of a high first-pass lung extraction of lidocaine in vivo (15–17). Experiments performed after brief infusions of bupivacaine in dogs (18) and prolonged infusions of lidocaine in sheep (11), together with the results of the present study, suggest that there is no elimination of these agents by the lung. Thus it would seem that the lung uptake of these agents results from distribution rather than metabolism.

There was no evidence of clearance of ropivacaine by the heart and brain; there was, however, evidence of some clearance by the splanchnic region drained by the portal vein. The arterial-hepatic vein blood ropivacaine concentration difference could not be attributed entirely to clearance by the liver; a small but significant amount of ropivacaine was extracted by the gut. It is not known by which mechanism the gut extracted ropivacaine. Previous work from this laboratory has shown that etidocaine is also extracted by the gut (19). It is known that sequestration of organic bases, e.g., meperidine (pK_a of 8.7), occurs due to diffusion of the un-ionized form across the gastric mucosa into the stomach cavity where the acidic medium causes trapping of the conjugate acids (20,21). By the same mechanism, the IV administration of lidocaine to pregnant ewes with fetal acidosis caused an increase of fetal blood lidocaine concentration (22). It would be expected that ropivacaine (pK_a of 8.07) (23) would readily diffuse across the gastric mucosa and thus be ion-trapped in the gastric contents. Although it may be subsequently reabsorbed from the gut, the high hepatic clearance would minimize the extent of ropivacaine recirculation.

Clearance by the kidneys of amide-type local anesthetics in humans is uniformly small, with mean fractions excreted unmetabolized into urine ranging from 0.01 to 0.03 (24). The small kidney clearance observed in this study by direct measurement and by urinary excretion indicates that ropivacaine is similar to the other agents.

It is often assumed that the measured TBCl of the amide-type local anesthetics can be accounted for by hepatic metabolism virtually exclusively (9). However, recent similar studies with lidocaine and bupivacaine have established that prolonged distribution into fat can be included in the measured value of TBCl (25,26) and is manifested as prolonged arterial-PVC concentration differences at essentially constant arterial blood drug concentrations (8). In the present study there was no significant arterio-PVC ropivacaine concentration difference. This result was unexpected given the chemical similarities of ropivacaine and bupivacaine; however, it is possible that there is a difference in the tissue uptake of the enantiomers of bupivacaine that accounts for this result. The mean sum of the measured regional clearances was 1.03 ± 0.38 L/min, a value essentially identical to the mean of the measured TBCl (1.00 ± 0.27 L/min). Thus, the TBCl of ropivacaine could be accounted for by the sum of the liver (0.85 ± 0.32 L/min), gut (0.09 ± 0.07 L/min), and kidney (0.04 ± 0.03 L/min) clearances.

From studies in dogs (4) and humans (5) it has been concluded that after IV infusion the TBCl of ropivacaine was slightly greater than that of bupivacaine. However, because a slightly larger dose of ropivacaine may be required to produce a nerve block of the same duration as bupivacaine (1,3,6,7), any pharmacokinetic advantage in the use of ropivacaine over bupivacaine may be minimal. If so, this finding would be consistent with our previous conclusion that, in sheep, bupivacaine and ropivacaine produced toxic central nervous and cardiovascular system effects in proportion to their anesthetic potencies (27,28).

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Epidural Droperidol and Morphine for Postoperative Pain

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NAJI P, FARSCHTSCHIAN M, WILDER-SMITH OH, WILDER-SMITH CH. Epidural droperidol and morphine for postoperative pain. Anesth Analg 1990;70:583–8.

Epidural morphine is effective in the treatment of postoperative pain, but the incidence of associated side effects is high. To assess a potential reduction of opioid side effects by droperidol, 4 mg morphine with either placebo or 2.5 mg droperidol was injected epidurally in a double-blind, randomized, postoperative trial. Forty patients undergoing hip replacement surgery were studied. The overall incidence of side effects during the first 24 h in the group receiving droperidol and morphine was less than 50% of that in the group receiving placebo and morphine ($P < 0.008$). Pruritus, emesis, nausea, urinary retention, and hypotension were diminished in the group with droperidol. No significant differences in duration or quality of analgesia were seen. Epidural injection of droperidol did not result in any local or systemic side effects.

Key Words: PAIN, POSTOPERATIVE—epidural droperidol, morphine. ANESTHETIC TECHNIQUES, EPIDURAL—droperidol, morphine. ANESTHETICS, INTRAVENOUS—droperidol. ANALGESICS, MORPHINE.

Postoperative pain relief is unsatisfactory in up to 60% of patients (1–4), and side effects of the analgesics given are common (5). Improved pain relief is often possible by optimizing and individualizing analgesic treatment (6). Protracted and satisfactory postoperative analgesia can be achieved with epidural morphine (5,7). Side effects, such as nausea, emesis, pruritus, and urinary retention commonly occur. Approximately 40% of patients given epidural morphine postoperatively vomit or experience nausea (5,8).

Droperidol is a dopamine-receptor antagonist that has shown reasonable antiemetic efficacy when given parenterally (9). Droperidol also has 5-hydroxytryptamine-antagonist, α_1-agonist, and weak α_2-agonist properties (10–12). 5-Hydroxytryptamine 3-receptor antagonists have shown considerable antiemetic potential in chemotherapy-induced vomiting (13,14). Droperidol may therefore act as an antiemetic by multiple mechanisms. A case report showed a possible antiemetic effect of epidurally injected droperidol (15).

Droperidol has been shown to enhance opioid analgesia in chronic pain patients (16–18). This action may be due to its α-agonist and dopamine-antagonist properties, both at spinal and supraspinal levels. α_2-Agonists, given parenterally or epidurally, are effective analgesics and potentiate opioid-induced analgesia (19–22). Spinal noradrenergic, inhibitory pain pathways are implicated in this mode of analgesia. Central and spinal descending, dopaminergic pathways have been demonstrated—ones that may be involved in pain modulation (23,24).

No local or systemic toxic effects of epidural droperidol have been reported except excessive sedation, which abated after dose reduction, and a reversible parkinsonoid syndrome after an overdose. The individual dosages used were between 1.25 and 5 mg epidurally.

The purpose of this study was to assess the reduction of side effects and the potentiation of analgesia of epidural morphine by epidural droperidol.

Methods

The study was performed in a single center. All anesthetic procedures and the documentation were carried out by two anesthesiologists and a small

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nursing team. Forty successive patients, aged between 30 and 80 yr, with an ASA physical status of I–III, who had been admitted for elective hip-replacement surgery, were randomized to receive either 4 mg morphine with 0.9% NaCl or 4 mg morphine with 2.5 mg droperidol (DHBP, kindly donated by Janssen Pharmazeutika, Baar, Switzerland) epidurally for postoperative analgesia (see Table 1 for patient data). Exclusion criteria included recent opioid medication, epilepsy, Parkinson's disease, excessive blood loss, or other intraoperative complications (including duration of operation >3 h), as well as the usual contraindications for epidural procedures. Midazolam (7.5 mg) was given 30–45 min preoperatively. Ringer's lactate (1000 mL) was infused before epidural blockade. The loss-of-resistance method was used to locate the epidural space at L-3 or L-4 in the lateral recumbent position. Lidocaine-CO_2 (3 mL) (Astra, Switzerland) was given as a test dose. After insertion of the epidural catheter, a further 3-mL dose of carbonated lidocaine was injected. After positioning on the operating table, and while surgical drapes were being applied, the last 3 mL of lidocaine was given. One hour later, the first half of the dose of 0.5% bupivacaine (Astra) was injected, followed, after 90 min, by the second half. The doses of bupivacaine used were calculated according to weight, age, and size to block segments T-5 to L-4.

Morphine with placebo or with droperidol was given 1.5 h after the last bupivacaine injection. This was usually done on admission to the recovery room. Repeat drug doses were given on demand. Ampules of droperidol or 0.9% NaCl were prepared for double-blind, coded use (Janssen Pharmaceuticals, Belgium). Heart rate, blood pressure, pain by verbal rating scale (VRS 0–4: 0 = none, 4 = excruciating), nausea (VRS 0–4), emesis (number of episodes), sedation (VRS 0–4), and other side effects—such as pruritus, urinary retention, and extrapyramidal signs (VRS 0–4)—were assessed by the same nursing team at hours 0, 2, and 4 after the first epidural injection of the study drugs, and thereafter every 4 h for a total of 24 h. Blood gas analyses were performed immediately before and approximately 5 h after injection of the study drugs. All additionally required medications and the time of further on-demand epidural injections were recorded.

Four hours postoperatively, patients were presented with a simple coordination and concentration task (Trieger test), which consisted of joining six numbered points on paper (25). Plasma samples for measurement of droperidol levels were obtained at approximately 1 and 4 h after the first injection of the study drugs. Droperidol concentrations were measured with a radioimmunoassay using antibodies against benzperidol (Janssen Pharmaceutical Analytic Laboratory, Belgium).

Table 1. Patient Characteristics

	Morphine/placebo ($n = 20$)	Morphine/droperidol ($n = 20$)
Age (yr)[a]	64 ± 11	65 ± 10
Sex (male/female)	7/13	8/12
Height (cm)[a]	165 ± 7	166 ± 9
Weight (kg)[a]	73 ± 14	70 ± 12
Creatinine (μmol/L)[a]	85 ± 18	84 ± 33

[a] Mean ± SD

Table 2. Intraoperative Epidural Anesthesia

	Morphine/ placebo ($n = 20$)	Morphine/ droperidol ($n = 20$)
Level of catheter insertion		
L2-3	1	0
L3-4	19	20
Upper limit of sensory block		
T-4	7	5
T-5	5	3
T-6	5	8
T-7	1	2
T-10	1	2
Intraoperative analgesia		
Satisfactory	20	20
Unsatisfactory	0	0

The detection limit was 0.4 ng/mL.

All patients gave oral informed consent, and the Hospital Ethics Committee gave its approval.

Statistical analysis was performed with χ^2 or Student's t-test. $P < 0.05$ was considered to be statistically significant. Mean values and standard deviations are shown.

Results

The two patient groups were demographically comparable (Table 1). There were no statistically significant differences in the extent and clinical efficacy of intraoperative anesthesia, in the requirements of additional intraoperative medications, or in the incidence of perioperative complications (Table 2).

Side Effects and Postoperative Course

Fourteen patients in the morphine/droperidol and 18 in the morphine/placebo group experienced side effects ($P = 0.11$). The average number of side effects

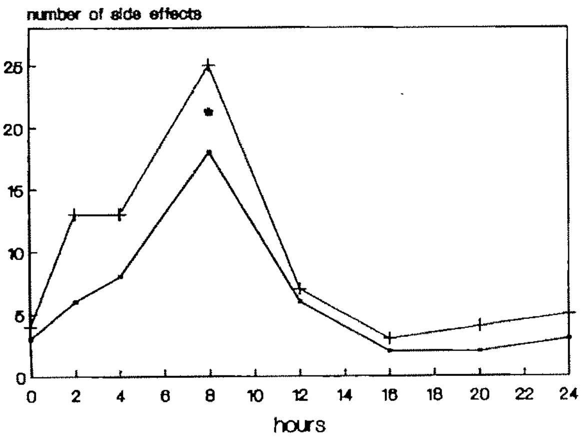

Figure 1. Total number of side effects in 40 postoperative patients given epidural morphine with either placebo (——+——) or droperidol (——■——). *$P < 0.008$.

Table 3. Incidence of Side Effects With Epidural Morphine/Droperidol and Morphine/Placebo

	Morphine/ placebo (n = 20)	Morphine/ droperidol (n = 20)	P
Nausea/vomiting	13 (65%)	7 (35%)	<0.05
Pruritus	11 (55%)	5 (25%)	<0.05
Urinary retention	8 (40%)	5 (26%)[a]	NS
Hypotension (<80/50 mm Hg)	4 (20%)	0	<0.05
Respiratory depression (5 h postinjection)	0	0	NS

NS = not significant.

The numbers given are patients with the side effect; percentages are shown in parentheses.

[a] Only 19 patients included: one patient had a urinary catheter inserted before surgery.

per patient was 1.8 ± 0.9 without droperidol and 0.9 ± 0.7 with droperidol ($P < 0.008$) (Figure 1). More patients with morphine/placebo experienced urinary retention, pruritus, nausea and vomiting, and hypotension (blood pressure < 80/50 mm Hg) (Table 3).

Significantly fewer patients vomited with droperidol than without during the 24-h observation period ($P < 0.05$) (Table 3). This difference was even more pronounced in the first 4 h after injection (3 vs 11 patients, respectively) ($P < 0.01$). The number of vomiting episodes in the 24-h period was reduced by almost 50% with droperidol (Figure 2). Fewer patients were nauseated with morphine/droperidol ($P < 0.05$) (Table 3), and the mean intensity of nausea was less than 50% of those given morphine/placebo (Figure 3). In both groups maximum nausea was seen 8 h postoperatively.

All patients in both groups had some initial sedation. In the first 2 h after epidural injection sedation was significantly greater in the group given droperidol ($P < 0.005$) and remained so until 4 h later.

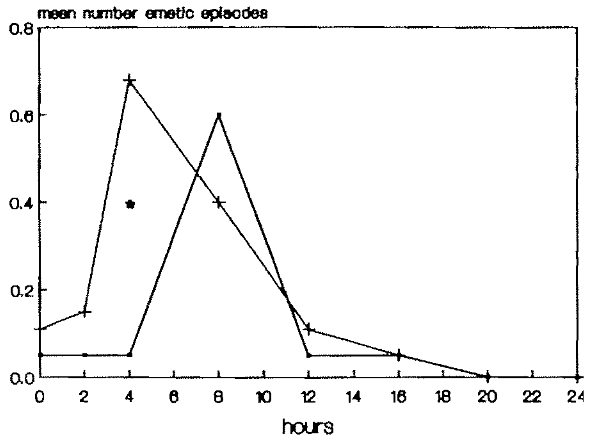

Figure 2. Mean number of emetic episodes in 40 postoperat patients given epidural morphine with either placebo (——+— or droperidol (——■——). *$P < 0.01$.

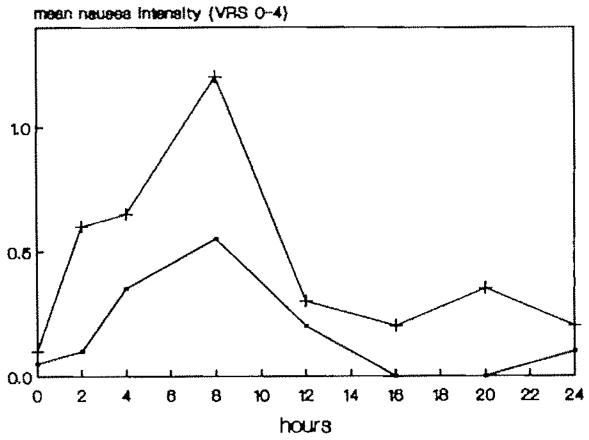

Figure 3. Mean intensity of nausea (VRS: 0–4) in 40 postoperat patients given epidural morphine with either placebo (——+— or droperidol (——■——).

Subsequently, the group given morphine/place was judged more sedated (Figure 4). Patients giv droperidol generally performed the Trieger test bet 4 h postoperatively than those given placebo inj tions (P = 0.087).

Pruritus occurred less often in patients given m phine/droperidol in the 24-h postoperative period < 0.05) (Table 3). Again, this difference was m significant in the first 4 h ($P < 0.01$). In both grou this side effect receded after approximately 12 (Figure 5).

Hypotensive episodes occurred in none of the patients with droperidol. Four of the 20 patie given morphine/placebo had hypotension 2–16 postoperatively. No other significant differences hemodynamic responses occurred. In both grou the heart rate increased postoperatively from 72 ± beats/min at the time of injection to 72 ± 12 beats/m 2 h and 86 ± 11 beats/min 24 h later with morphi

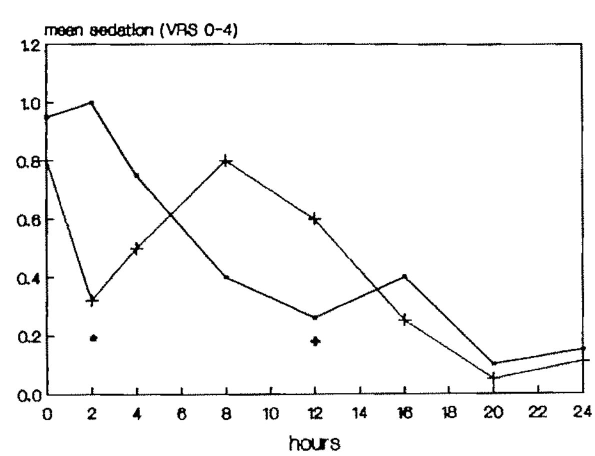

Figure 4. Mean sedation score (VRS: 0–4) in 40 postoperative patients given epidural morphine with either placebo (——+——) or droperidol (——■——). $^*P < 0.005$; $^+P = 0.087$.

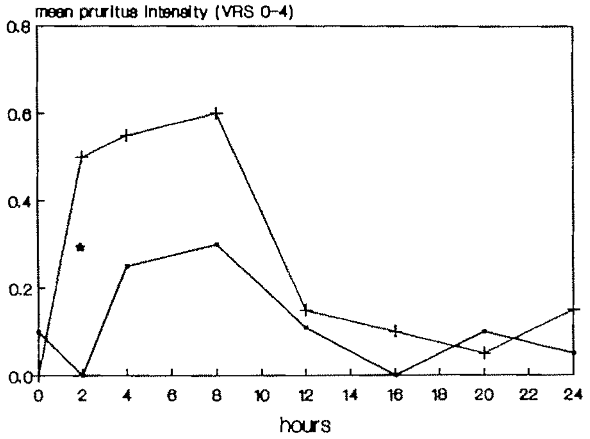

Figure 5. Mean intensity of pruritus (VRS: 0–4) in 40 postoperative patients given epidural morphine with either placebo (——+——) or droperidol (——■——). $^*P < 0.03$.

droperidol, and from 69 ± 10 beats/min to 72 ± 12 and 86 ± 14 beats/min with morphine/placebo, respectively. Mean systolic and diastolic pressures at the time of injection were 116 ± 19 and 75 ± 11 mm Hg with droperidol and 113 ± 13 and 74 ± 6 mm Hg without droperidol, respectively. These values decreased slightly to 112 ± 17 and 68 ± 12 mm Hg, and 110 ± 14 and 70 ± 11 mm Hg 2 h later, respectively, and then gradually increased to stabilize near 125/75 mm Hg in both groups.

No significant differences in blood gas tensions occurred.

Pain Intensity

Pain reached maximum intensity 4 h postoperatively in patients given morphine/droperidol (VRS = 0.55), and 4 (VRS = 0.5) and 20 (VRS = 0.65) h postoperatively in patients given morphine/placebo (Figure 6). Pain ratings in patients given morphine/placebo were higher than in those given droperidol after 16 h. However, there was no difference in the mean 24-h rating of pain intensity (VRS = 0.39 ± 0.3 morphine/droperidol, 0.34 ± 0.3 morphine/placebo). In each group four patients reported no pain during the study period.

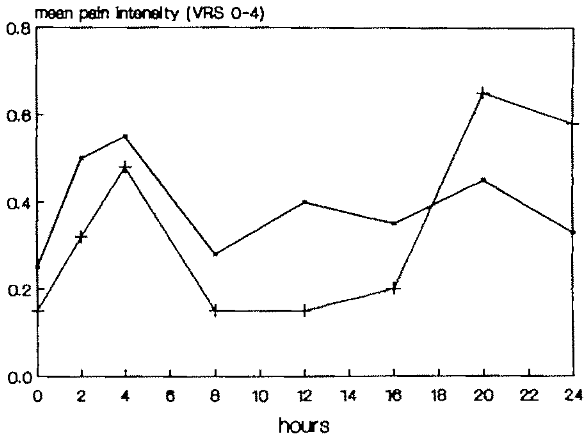

Figure 6. Mean pain intensity score (VRS: 0–4) in 40 postoperative patients given epidural morphine with either placebo (——+——) or droperidol (——■——). See text and Table 3 for additional analgesics given.

Table 4. Additional Postoperative Medications

	Morphine/ placebo (n = 20)	Morphine/ droperidol (n = 20)
Antiemetics	10 (8)	4 (3)
Cardiovascular	3 (2)	2 (2)
Other analgesics	2 (2)	3 (3)
Miscellaneous (cimetidine, antispasmodics, potassium)	4 (3)	3 (3)

The number of drug applications is shown; the number of patients is shown in parentheses.

Additional Medication

Ten patients given morphine/droperidol and 12 given morphine/placebo required additional postoperative medication (Table 4).

Repeat On-Demand Dosing

During the 24-h study period 5 patients given morphine/droperidol (one patient twice) and nine patients given morphine/placebo required a second epidural injection for pain relief. These second injections occurred an average of 17.7 and 17.3 h after the first injections of droperidol and placebo, respectively.

Plasma Droperidol Levels

Plasma samples were available from 10 patients. Four were from patients given droperidol. All other samples were mistakenly stored as whole blood and could not be used. Mean plasma droperidol concentrations 45 min after epidural injection were 16 ng/mL (range 13.2–19.2). After approximately 300 min, the plasma levels were between 4.3 and 6.7 ng/mL. An approximate plasma half-life of 2.8 h and a concentration peak of 21.5 ng/mL were calculated.

Discussion

The addition of epidural droperidol to epidural morphine in the management of postoperative pain reduced the incidence and severity of morphine-related side effects. The workload for the nursing staff was hereby noticeably diminished.

Opioid side effects, excluding sedation, were significantly lower in the first 4 h after epidural injection of droperidol than after epidural injection of placebo. This duration of action corresponds well with the estimated plasma half-life of 2.8 h of droperidol. The maximum plasma concentration of 21.5 ng/mL was about half the concentration expected after intravenous administration of 2.5 mg droperidol (26). The action of epidural droperidol cannot, however, be attributed only to systemic distribution, as the beneficial effects on nausea and pruritus lasted much longer. These prolonged effects may be due to direct spinal and supraspinal (chemoreceptor trigger zone, vomiting center) actions on dopamine, 5-hydroxytryptamine, and α-adrenergic pathways (27). Nausea and vomiting are partly mediated by visceral nociception, and the inhibition of afferent spinal input may be an important factor in antiemetic treatment (15,27).

Pain scores were lower with epidural droperidol toward the end of the study period, and fewer on-demand epidural injections were required than with placebo, but a significant enhancement of the analgesic effect of morphine by epidural droperidol was not detected with our 24-h study design. This may be due to differences in the duration of action of droperidol and morphine and the generally satisfactory analgesia for 12–18 h with epidural morphine alone. Small improvements in the duration or depth of analgesia, seen in a prolonged study period (16), would not reach significance in a single 24-h period. Studies with shorter-acting opioids would be more suitable for assessing this aspect of the postoperative analgesic potential of droperidol.

Epidural droperidol in doses of 2.5 mg did not result in any appreciable toxicity, except possibly greater sedation. However, despite the higher sedation scores, the Trieger test was performed better by the patients given droperidol and morphine. The conflicting results illustrate the difficulties in assessing sedation in patients given neuroleptics. These compounds induce a state of quiescence, with reduced movements, diminished expressed anxiety, and a degree of indifference to the surroundings (28). This could easily be mistaken for sedation. In an earlier study, sedation in 6 of 22 patients occurred at mean droperidol doses of 4.7 mg, but not at lower doses of 2.2 mg (16).

No other side effects of epidural droperidol have been reported, except a Parkinson syndrome seen after repeated accidental injections of 30 mg, which was reversed with biperiden (16). A postmortem examination performed in a man after 4 mo of continuous treatment with epidural droperidol showed no evidence of local toxicity (16).

In conclusion, epidural droperidol significantly reduced the side effects of epidural morphine.

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Mass Spectrometric Measurements of Oxygen Uptake During Epidural Analgesia Combined With General Anesthesia

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VIALE JP, ANNAT GJ, TISSOT SM, HOEN JP, BUTIN EM, BERTRAND OJ, MOTIN JP. Mass spectrometric measurements of oxygen uptake during epidural analgesia combined with general anesthesia. Anesth Analg 1990;70:589–93.

Oxygen uptake was measured using a mass spectrometer system in 12 patients scheduled for abdominal surgery who intraoperatively were mechanically ventilated with 50% nitrous oxide and given continuous intravenous infusions of methohexital (3.5 $mg\cdot kg^{-1}\cdot h^{-1}$) plus repeated epidural injections of lidocaine. At the end of the surgical procedure, meperidine (0.7 mg/kg) was epidurally injected in six patients (group A). The other six patients (group B) received no epidural injections during the first 2 h after surgery. Intraoperatively, oxygen uptake decreased in both groups by an average of 28%. Within the first two postoperative hours, clear-cut differences among the two groups arose. Patients in group A had smoother increases in oxygen uptake and core temperatures, greater cardiovascular stability as reflected by the rate-pressure product, and no visible shivering. We suggest that epidural meperidine given immediately at the end of a surgical procedure might be beneficial, especially, perhaps, in patients with impaired cardiac function.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—meperidine. ANALGESICS, MEPERIDINE—epidural. PAIN, POSTOPERATIVE—epidural meperidine. OXYGEN, UPTAKE—postoperative.

The perioperative period is associated with marked changes in total body oxygen uptake ($\dot{V}o_2$) (1). During anesthesia, $\dot{V}o_2$ decreases. Postoperatively, $\dot{V}o_2$ increases. The latter may represent a potential hazard in patients with impaired cardiac function. We hypothesized that these changes can be influenced by anesthetic management. Accordingly, the present study was conducted with two purposes. The first was to examine the effects of epidural analgesia combined with general anesthesia on intraoperative $\dot{V}o_2$. This anesthetic technique facilitates postoperative analgesia and has been suggested as having beneficial effects on operative outcome (2). The second purpose was to examine modifications of $\dot{V}o_2$ induced by the administration of epidural narcotics in the immediate postoperative period.

Methods

Twelve patients scheduled to undergo abdominal surgery were enrolled in the study after obtaining institutional approval and informed consent. All patients were ASA physical status I or II, and those with known or suspected coronary artery disease were excluded from the study. Relevant clinical patient data are outlined in Table 1. Patients were premedicated with orally administered hydroxizine (1.5 mg/kg), and an epidural catheter was placed before anesthesia. Anesthesia was induced by intravenous methohexital (2 mg/kg), the trachea was intubated after topical anesthesia, and ventilation was controlled with an inspired gas mixture of oxygen (30%), nitrogen (20%), and nitrous oxide (50%). Inspired gases were heated and humidified. The tidal volume was set at 10 mL/kg and the ventilatory rate at 12 breaths/min. Maintenance of anesthesia was provided by a continuous infusion of methohexital (3.5 $mg\cdot kg^{-1}\cdot h^{-1}$). All patients received epidural injections of 2% lidocaine to achieve and maintain surgical anesthesia and muscle relaxation, and all were lying on a heated water mattress. Warmed packed red blood cells were given when required. A 5% glucose

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Table 1. Patient Characteristics

Patient No.	Age (yr)	Weight (kg)	BSA (m^2)	Surgical procedure	Duration of surgery (min)
Group A					
1	75	70	1.73	Left colectomy	360
2	37	85	1.92	Gastrectomy	300
3	32	35	1.24	Total colectomy	320
4	50	65	1.76	Left colectomy	240
5	43	58	1.66	Abdominoperineal resection	300
6	68	72	1.89	Left colectomy	240
Mean ± SE	51 ± 7	64 ± 7	1.70 ± 0.1		293 ± 19
Group B					
1	64	52	1.56	Left colectomy	240
2	46	69	1.75	Left colectomy	240
3	57	65	1.71	Abdominoperineal resection	310
4	75	60	1.60	Right colectomy	240
5	76	72	1.78	Gastrectomy	270
6	37	63	1.79	Left colectomy	300
Mean ± SE	59 ± 6	63 ± 3	1.69 ± 0.03		267 ± 13

BSA, body surface area.

solution was given at a constant rate of 3 $mL \cdot kg^{-1} \cdot h^{-1}$, and warmed Ringer's solution was given as intravenous maintenance fluid. At the end of the surgical procedure, meperidine (0.7 mg/kg) was injected epidurally in six patients (group A). The other six patients (group B) received no epidural injections during the first 2 h after surgery but were given 0.1 mg/kg morphine subcutaneously. Thereafter, patients in both groups received the same postoperative care, including epidural administration of narcotics, continuous monitoring, and physiotherapy.

Throughout the study, core temperature, heart rate, and arterial pressure were measured continuously. Pulmonary gas exchange was recorded first during the 30 min before anesthesia using a face mask and a Laerdal valve allowing for separation of inspired and expired gases, then during the first 4 h of anesthesia and again during the first 2 h after anesthesia while the patients were still being mechanically ventilated. Description and validation of the mass spectrometer system used for these measurements during general anesthesia (3) are summarized as follows. Pulmonary gas exchange was computed according to the following equations:

$$\dot{V}O_2 = \dot{V}E\,(FIO_2 \times FEN_2/FIN_2 - FEO_2),$$

$$\dot{V}CO_2 = \dot{V}E \times FECO_2,$$

$$RQ = \dot{V}CO_2/\dot{V}O_2,$$

where FI and FE are the fractional concentrations of inspired and expired gases, respectively, $\dot{V}E$ is the expired flow, and RQ is the respiratory quotient. The equation used for calculation of $\dot{V}O_2$ is valid even in the presence of anesthetic gases (4). Gas samples were drawn from the patient's mouthpiece for 60 s while FIO_2 and FIN_2 were measured by a mass spectrometer (Perkin Elmer MGA 1100). The input valve of the mass spectrometer was then automatically switched for another 60-s period to draw gas samples from a 4-L expiratory mixing chamber to measure FEO_2, $FECO_2$, and FEN_2. During these two sequences, flow-rate signals from a pneumotachometer were sampled and integrated to compute expired minute volume. Corrections of the flow signal were made to take into account the composition of the expired gas and to convert the results into STPD conditions (3). At the end of this 2-min measurement cycle, $\dot{V}O_2$ (STPD), $\dot{V}CO_2$ (STPD), and RQ were computed, and the results were stored. The gas exchange data obtained during the 15 min after the beginning and the end of anesthesia were disregarded to take into account changes in body nitrogen stores following step changes in FIN_2 (3). Results are given as mean ± SE. The statistical significance of changes associated with epidural administration of the narcotic was examined by the use of analysis of variance with repeated measurements. Multiple comparisons of mean values were made by the Duncan multiple range test. A P value <0.05 was considered statistically significant.

Results

Figure 1 shows time-courses of changes in $\dot{V}O_2$, esophageal temperature, and rate-pressure product averaged over 15-min periods. Preoperative values of

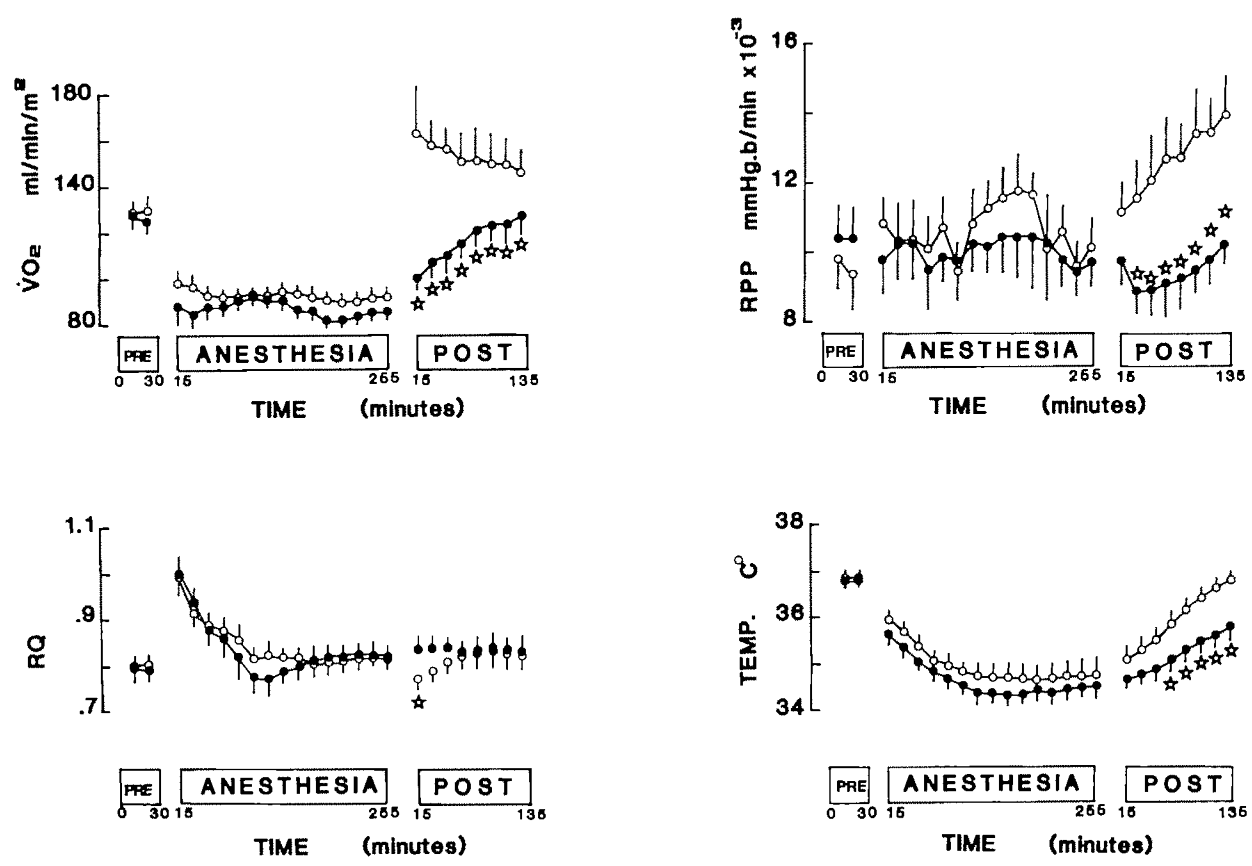

Figure 1. Changes in rate-pressure product (RPP), oxygen uptake ($\dot{V}O_2$), esophageal temperature (Temp), and respiratory quotient (RQ) before (PRE), during (ANESTHESIA), and after (POST) epidural analgesia combined with general anesthesia. *Closed circles*, six patients (group A) given 0.7 mg/kg meperidine epidurally at the end of the surgical procedure. *Open circles*, six patients (group B) who received no epidural injection during the first 2 h after surgery. ☆Significantly different ($P < 0.05$) for the comparison between groups.

$\dot{V}O_2$ were similar in both groups. After induction of anesthesia, $\dot{V}O_2$ decreased an average of 28% in the 12 patients, and thereafter remained stable throughout the anesthesia. In the postoperative period, $\dot{V}O_2$ increased steeply soon after the end of anesthesia in group B, whereas in group A it gradually increased toward preoperative values. Clinically evident shivering was observed in four patients in group B and in none of group A. During this period the two patients in group B who did not shiver had lower values of $\dot{V}O_2$ than the other patients of the same group. In both groups, RQ increased soon after the beginning of anesthesia and then decreased, thereafter returning intraoperatively to preoperative values about 60 min after induction. No change in RQ was subsequently observed, except for a transient decrease (in group B patients only) at the beginning of the postoperative period. In the two groups there were similar and parallel decreases in esophageal temperature during anesthesia, more pronounced during the first hour of anesthesia. Postoperatively, the esophageal temperature increased in both groups, but the increase in temperature was slower in onset in group A than in group B. The rate-pressure product remained stable throughout the study except in the postoperative period of group B during which it increased.

Discussion

In this study, $\dot{V}O_2$ was continuously measured using an open-circuit collection technique. This was made possible by use of equipment allowing simultaneous multiple gas analysis and on-line computation of gas exchange. Use of nitrogen as a tracer gas to compute inspired volume from the measurement of expired volume proved unreliable after step changes in F_{IN_2} associated with the beginning and the end of anesthesia. So the initial gas exchange data acquired during these two periods had to be rejected. At that time, nitrogen body stores are transiently in an unsteady state, and the computation of $\dot{V}O_2$ from the equation described above leads to a systematic error. This error has been found, however, using a dynamic model of nitrogen body stores (5), to be negligible 15 min after abrupt changes in F_{IN_2} (3).

Preoperative $\dot{V}O_2$ values in our premedicated supine patients were close to those previously measured in resting humans (6) and are indicative of a normometabolic state. The decrease in $\dot{V}O_2$ that we observed after the induction of anesthesia is of the same magnitude as the one found by others in patients given balanced anesthesia with narcotics and muscle relaxants (1,3,7,8). In addition, epidural anesthesia of the same extent as that used in the present study has been found to be associated with minimal effects on $\dot{V}O_2$ (9). Thus, most of the decrease in $\dot{V}O_2$ in our patients could be ascribed to the use of intravenous anesthetic, including anesthesia-induced sleep (10), with reduction in the metabolism (11) and, perhaps, decreases in body temperature. In this regard, difference in times of onset of the decrease in temperature and decrease in $\dot{V}O_2$ in this study suggests that the change in temperature is the consequence rather than the cause of the change in metabolic rate. The increase in RQ measured in both groups of patients during the first hour of anesthesia is in keeping with our previous observations under similar conditions (3). It can be ascribed to transient alveolar hyperventilation after the institution of mechanical ventilation. With alveolar hyperventilation, carbon dioxide body stores decrease and the amount of carbon dioxide eliminated in the expired gas transiently exceeds that produced by the organism. This effect, combined with the immediate decrease in $\dot{V}O_2$ after induction, explains the transient increase in RQ.

The postoperative increase in oxygen consumption was slower and delayed in patients who were given epidural meperidine than it was in patients not given epidural meperidine. At least two main factors may account for this. First, the neuroendocrine stress response associated with return to consciousness and the degree of pain were probably reduced in the meperidine group (12). Indeed, a reduced catecholamine release could contribute to a lower postoperative metabolic rate (13). Similarly, a lower rate-pressure product and thus a lower myocardial oxygen consumption might have contributed to the lower $\dot{V}O_2$ level (14). However, myocardial oxygen consumption represents only 10%–15% of the total body oxygen consumption (15). Thus, although a decrease in myocardial metabolic demand might be of importance in patients with a poor coronary reserve, it was unlikely to play a major role in determining the difference in $\dot{V}O_2$ between the two groups in our study. The second factor involved in the delayed increase in $\dot{V}O_2$ associated with meperidine was the absence of shivering, a well-known cause of increased $\dot{V}O_2$ in the postoperative period (16). In this regard, the difference of behavior between shivering and nonshivering patients in group B emphasizes the role of this factor. Intravenous meperidine has been shown to be effective in the treatment of postanesthetic shivering by the intravenous route (17): meperidine also appears useful for prevention of shivering by the epidural route.

As previously observed by others (17), we found the postoperative core temperature to be generally lower in patients who received meperidine than in nontreated patients, which might also represent a factor contributing to their lower $\dot{V}O_2$. However, it must be emphasized that the difference in $\dot{V}O_2$ levels between the two groups was obvious from the beginning of the postoperative period, when all patients had still similar core temperatures (Figure 1).

In group B patients, RQ transiently decreased during the first 30 min after the end of anesthesia. It is well known that in the case of a rapid change in metabolic rate with no change in minute ventilation, the rate of change in $\dot{V}CO_2$ is slower than the rate of change in $\dot{V}O_2$ because of different exchange rates of oxygen and carbon dioxide body stores (18). In our patients, the abrupt increase in $\dot{V}O_2$ combined with a slower increase in $\dot{V}CO_2$ explains the transient decrease in RQ.

In conclusion, during the first two postoperative hours, the increase in $\dot{V}O_2$ toward preoperative values is made smoother and less abrupt by a single epidural injection of meperidine. Although the duration of this salubrious effect during the subsequent hours cannot be established from the results of the present study, epidural meperidine given at the end of a surgical procedure might be of value in patients with limited cardiac reserve.

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Respiratory Effects of Expiratory Flow-Resistive Loading in Conscious and Anesthetized Humans

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ISONO S, NISHINO T, SUGIMORI K, MIZUGUCHI T. Respiratory effects of expiratory flow-resistive loading in conscious and anesthetized humans. Anesth Analg 1990;70:594–9.

The response of breathing patterns to increased expiratory resistance is not only of physiologic interest, with respect to the control of breathing, but also of clinical interest because of its clinical relevance to obstructive diseases such as asthma and emphysema. To elucidate the response of breathing patterns to increased expiratory resistance during anesthesia, the respiratory effects of expiratory flow-resistive loading on breathing patterns were studied in 15 conscious and 10 lightly anesthetized subjects. Inspiratory time, expiratory time, respiratory frequency, inspiratory duty cycle, tidal volume, minute ventilation, and mean inspiratory flow rate were determined from a respiratory inductive plethysmograph. End-tidal CO_2 *was continuously recorded. In awake subjects, respiratory frequency was reduced without change in tidal volume or mean inspiratory flow rate, and minute ventilation was significantly decreased; the synchrony between rib cage and abdomen wall motion was well maintained during the loads. In contrast, in anesthetized subjects, respiratory frequency was reduced with remarkable increases in tidal volume, mean inspiratory flow rate, and minute ventilation, whereas coordination between rib cage and abdomen compartments was disturbed. End-tidal* CO_2 *did not change in conscious subjects, but it increased in anesthetized subjects during the loads. These results indicate that there are differences between conscious and anesthetized subjects in breathing patterns during expiratory loading, and suggest that the ability to coordinate rib cage–abdomen wall motion is easily disturbed during anesthesia in patients with expiratory flow limitation.*

Key Words: VENTILATION, EXPIRATORY RESISTANCE—effect of anesthesia.

In response to added loads such as external elastic or resistive load, human subjects can change their respiratory patterns to stabilize ventilation while minimizing the work of breathing. When the load is so great it cannot be compensated for by a subject's own efforts, ventilatory stability is lost and respiratory fatigue may ensue, leading to respiratory failure.

The effects of anesthesia on load compensation have been studied by many investigators (1–5). However, disagreement exists as to the effects of anesthesia on load compensation. For instance, Nunn and Ezi-Ashi (1) studied the effects of the threshold and tubular resistances during halothane-nitrous oxide anesthesia and found that reflex compensation for resistance to breathing is well maintained during anesthesia. On the other hand, Margaria et al. (2) reported that, in the conscious state, progressive tidal volume compensation from the first to the fifth loaded breath was greater than during anesthesia, probably reflecting a decreased chemosensitivity during anesthesia. Similarly, Whitelaw et al. (5) reported that the load compensatory responses to the inspiratory flow-resistive load observed in conscious subjects is absent in anesthetized subjects. Most of these studies, except for the study of Nunn and Ezi-Ashi (1), were concerned with the effects of inspiratory loading, and little information is available as to the effects of anesthesia on the responses to expiratory flow-resistive loads in humans. Furthermore, no information, to our knowledge, is available about thoracoabdominal wall motion in the presence of expiratory loads. Accordingly, in the present study we investigated the ventilatory responses to expiratory flow resistors both in conscious and anesthetized subjects while measuring rib cage (RC)–abdomen

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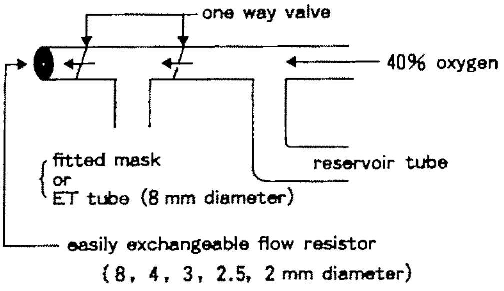

* Resistances at the flow of 20 ℓ/min *

flow resistors (mm)	8	4	3	2.5	2
resistances ($cmH_2O/\ell/s$)	9	47	116	189	459

Figure 1. Experimental equipment showing the breathing circuit and the values of expiratory resistances. Separation of the inspiratory and expiratory lines is achieved by one-way valves, while inspired oxygen concentration is maintained at 40% in both groups. Five different sizes of easily exchangeable flow resistors are placed in the expiratory line.

(AB) wall motion with respiratory inductive plethysmography.

Methods

Fifteen operating room nurses (consciousness group [C group]) aged 21–25 yr (22.1 yr ± 0.3 [mean ± SEM]) and 10 patients undergoing elective surgery (anesthesia group [A group]) aged 16–55 yr (36.7 ± 3.8 yr) were studied in the supine position. The average weights and heights of the nurses in the C group were 51.4 ± 2.0 kg and 156 ± 1.6 cm, and those of the patients in the A group were 60.8 ± 1.7 kg and 160.5 ± 2.6 cm. None of the subjects had clinical evidence of respiratory disorders, and all had normal ventilatory function. The protocol of the study was approved by the ethics committee of our hospital, and informed consent was obtained from each subject.

The experimental apparatus is shown in Figure 1. Five different sizes of easily exchangeable flow resistors (8.0, 4.0, 3.0, 2.5, and 2.0 mm in diameter) were placed in the expiratory line. Their expiratory resistances are shown in Figure 1. Inspiratory resistance in this circuit is 9 cm H_2O at a flow of 20 L/min. The inspired oxygen concentration was maintained at 40% in both groups. Ventilation was measured with computer-assisted respiratory inductive plethysmography (Non-Invasive Monitoring System, Respigraph) that was calibrated using a natural breathing, single posture method based on isovolume equation principles (6) and that provided reasonably accurate measurements even during loaded breathing (7). End-tidal CO_2 was continuously monitored with a CO_2 gas analyzer (Engström, ELIKA), and all respiratory variables were averaged over 5-min periods and were recorded by a modified line printer (Hewlett-Packard, Thinkjet).

Subjects in the C group breathed a gas mixture of oxygen (8 L/min) and air (24 L/min) through the 8.0-mm resistive bore in a quiet operating room for about 10 min after facial masks were tightly fitted using headbands. Studies were started when the subjects' breathing patterns were stable.

Patients in the A group were premedicated 30 min before the induction of anesthesia with 0.5 mg atropine and 50 mg hydroxyzine intramuscularly. All studies were conducted before the beginning of surgery. Anesthesia was induced by intravenous diazepam (0.2–0.3 mg/kg) and thiamylal (4–5 mg/kg) followed by intravenous succinylcholine (1 mg/kg). A cuffed endotracheal tube (8 mm ID) was then inserted after the trachea was sprayed with 2 mL of 4% lidocaine. Anesthesia was maintained with enflurane (0.5%) mixed with 4 L/min of oxygen and 6 L/min of nitrous oxide. After spontaneous respiration had returned, the endotracheal tube of each patient was connected to an experimental apparatus incorporated into an anesthetic circuit. The studies were then started.

The experimental protocol was as follows. After the breathing pattern was stable with an 8.0-mm resistor, baseline ventilation for 5 min (control measurement) was recorded, after which the expiratory resistive load was increased in four steps by changing the size of the resistor. After a change in the size of the resistor, 4–9 min were allowed for a stable state to be reached before any measurement was made. Ventilatory variables were then recorded for 5 min.

The measured variables included respiratory rate (f), inspiratory time (T_I), expiratory time (T_E), inspiratory duty cycle (T_I/T_{tot}), tidal volume (V_T—% baseline), minute ventilation (V_I—% baseline), mean inspiratory flow rate (V_T/T_I—% baseline), percentage of rib cage contribution to the tidal volume (%RC), total compartmental displacement to tidal volume (TCD/V_T), and end-tidal P_{CO_2} (P_{ETCO_2}). Total compartmental displacement (TCD) is the sum of the area under the RC and AB compartmental displacements irrespective of algebraic sign. The TCD/V_T is derived by dividing the TCD by the area under the inspiratory SUM (V_T) wave form. When RC and AB are in complete synchrony, TCD/V_T = 1.00. Any timing or phase delay between the RC and AB compartments will increase the TCD/V_T, as seen in patients with chronic obstructive pulmonary disease (8,9).

Statistical analysis was performed using a two-way analysis of variance and Tukey's test. Some results were also analyzed using Student's *t*-test. All values

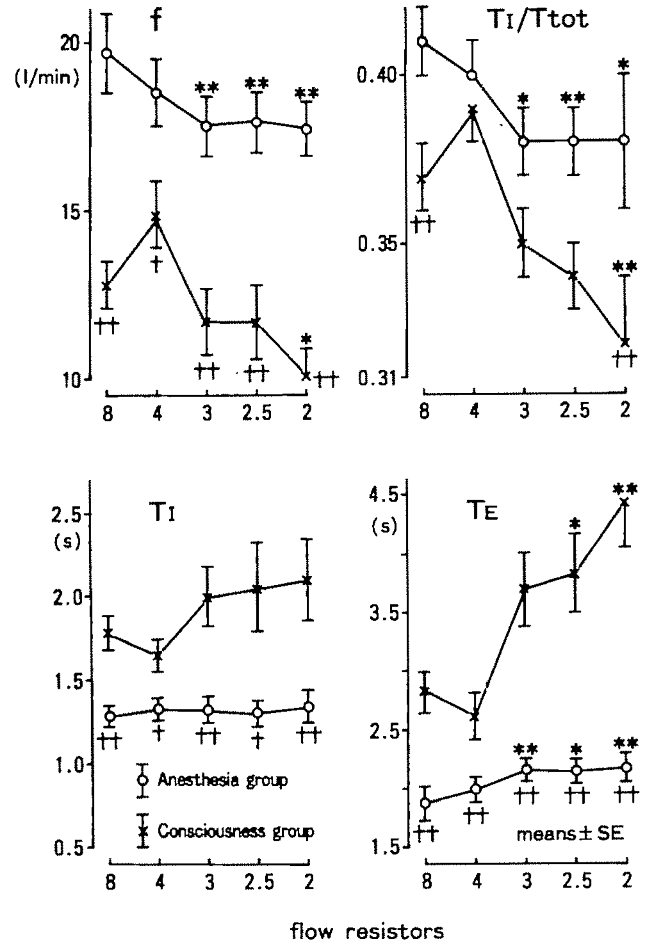

Figure 2. The effects of expiratory flow-resistive loads on respiratory frequency (f), inspiratory duty cycle (T_I/T_{tot}), inspiratory time (T_I), and expiratory time (T_E). *Open circles* represent data from anesthetized and *crosses* data from conscious subjects. Significantly different from values during breathing with 8.0-mm resistor: $^*P < 0.05$; $^{**}P < 0.01$. Significant difference between the two groups: $^{\dagger}P < 0.05$; $^{\dagger\dagger}P < 0.01$.

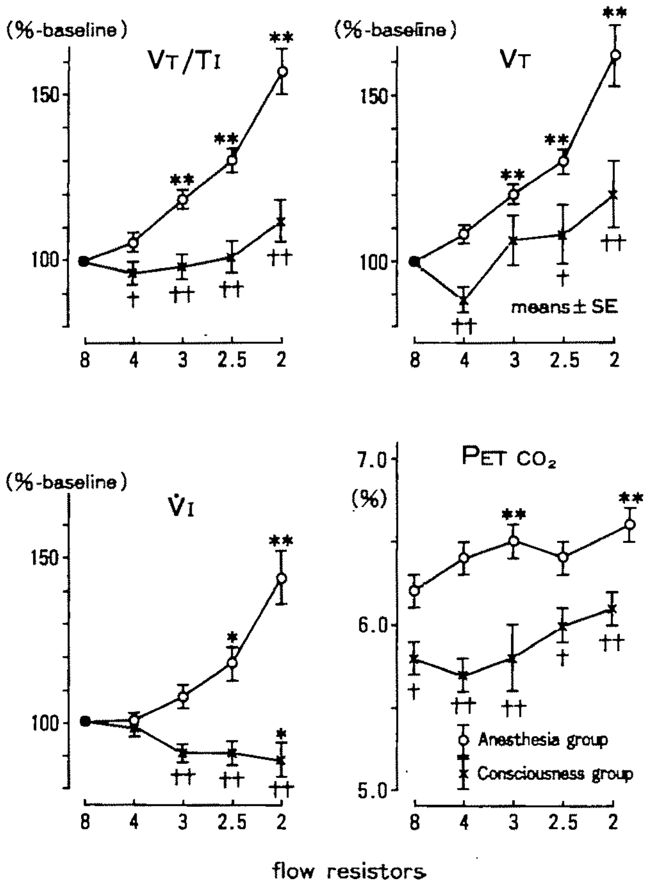

Figure 3. The effects of expiratory flow-resistive loads on mean inspiratory flow (V_T/T_I), tidal volume (V_T), minute ventilation (V_I), and end-tidal P_{CO_2} (P_{ETCO_2}). See legend of Figure 2 for further explanations.

are expressed as mean ± SEM, and $P < 0.05$ was considered to be statistically significant.

Results

Respiratory Times

In both the A and C groups, breathing frequency progressively decreased as the levels of expiratory load were increased (Figure 2). However, patients in the A group had a greater breathing frequency than did subjects in the C group at all levels of expiratory loads. The decrease in breathing frequency during increased expiratory loads was due solely to prolongation of T_E; T_I showed little or no change. Although the inspiratory duty cycle significantly decreased at severe levels of expiratory loads in both groups, the decrease in the C group was more pronounced than that in the A group.

Ventilatory Volume and End-Tidal CO₂ Concentration

With increasing expiratory loads there were progressive increases in V_T/T_I, V_T, and V_I in the A group, but no such responses were observed in the C group (Figure 3). Despite the increase in V_I in the A group, P_{ETCO_2} increased significantly. In contrast, there was no significant change in P_{ETCO_2} in conscious subjects.

Thoracoabdominal Wall Motion

Total compartmental displacement divided by tidal volume, an indicator of phase delay between the RC and AB compartments (Figure 4) (8,9), significantly increased when the resistor with a 2.0-mm diameter was applied in the A group. Three patients of the A

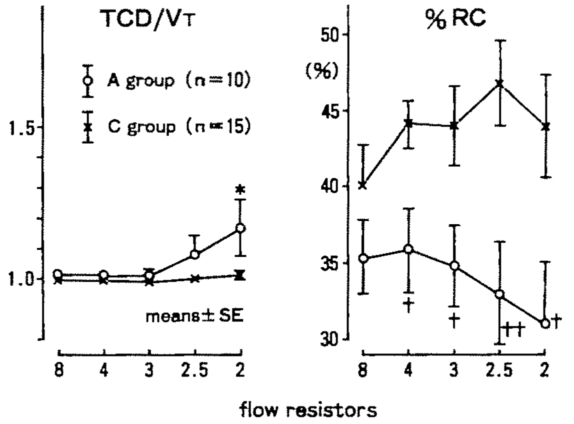

Figure 4. The effects of expiratory flow-resistive loads on the ratio between total compartmental displacement and tidal volume (TCD/V_T) and percentage of rib cage contribution to the tidal volume (%RC). See legend of Figure 2 for further explanations.

group had values of TCD/V_T greater than 1.20, and one of them showed respiratory alternans, a clinical sign of inspiratory muscle fatigue (10). On the other hand, subjects in the C group had no change in TCD/V_T at any level of expiratory load.

The subjects in the C group had a greater %RC than did patients in the A group throughout the experiment. This suggests that the former had a tendency to compensate for expiratory loads mainly by increasing intercostal muscle activity, whereas the latter did so mainly by increasing diaphragm activity.

Discussion

In the present study we demonstrated that considerable changes in breathing patterns occur during expiratory loads in both conscious and anesthetized subjects. The major finding in the present study is that in anesthetized subjects, expiratory resistive loading increases respiratory drive, whereas respiratory timing is little affected. These observations merit consideration in more detail.

Respiratory Cycle

In both awake volunteers and anesthetized patients, breathing frequency and the inspiratory duty cycle progressively decreased when expiratory flow-resistive loads were applied. These decreases were mainly due to prolongation of T_E and not to changes in T_I. Although the underlying mechanisms are not entirely clear, two possible mechanisms may be responsible for the increase of T_E. First, mechanical flow limitation by severe expiratory resistances may simply prolong the expiratory time. Second, assuming that during severe expiratory loads lungs are inflated enough to stimulate pulmonary stretch receptors, it is possible that the Hering–Breuer reflex might contribute to the prolongation of T_E observed in the present study. In this context, there is evidence that in humans the Hering–Breuer inflation reflex is present only with inflation volumes considerably above the resting tidal volume range (11).

The prolongation of T_E and decrease in T_I/T_{tot} observed in our study may play some role in preventing the diaphragm from fatigue during strenuous breathing due to resistive loading. In fact, the duty cycle has recently been shown to be an important determinant of respiratory muscle fatigue (12).

Respiratory Output

We used V_T/T_I to assess respiratory drive. Employment of this index, however, poses certain problems in this setting. V_T/T_I is considered to be an insensitive index for respiratory center output when there are changes in respiratory mechanics. Despite this potential limitation, an increased value of V_T/T_I in response to expiratory loads indicates elevated respiratory drive because changes in respiratory mechanics occurring during expiratory loading underestimate rather than overestimate respiratory drive. In light of this, the finding that V_T/T_I progressively increased with increasing expiratory loads in anesthetized patients while no such change occurred in conscious subjects indicates that the respiratory drive response to added expiratory loads is more pronounced in an anesthetized state than in the conscious state. The increase in respiratory drive observed in an anesthetized state cannot be entirely attributed to an increase in chemical drive, because P_{ETCO_2} varied by only 2–3 mm Hg from control values. Thus, mechanisms other than chemical control of breathing may be responsible for changes in respiratory drive during added expiratory loads. The discrepancy between anesthetized and conscious states may be related to the loss of consciousness. It is possible that voluntary/behavioral control of breathing is an important factor that determines the ventilatory response to added expiratory loads.

Coordination Between Rib Cage and Abdomen Compartments

Cohen et al. (10) suggested that the abnormalities of respiratory movements including respiratory alternans and abdominal paradoxic movement might be reliable clinical signs of inspiratory muscle fatigue in patients being weaned from mechanical ventilation. Similar findings were reported in patients with chronic obstructive pulmonary disease (8,13) and in patients with symptomatic asthma (8,14,15). These findings indicate that loss of coordination of thoracoabdominal wall motion may be a characteristic sign of respiratory muscle fatigue. In our study we found that as the expiratory resistance increased, there was a significant increase in TCD/V_T in anesthetized patients, whereas no change in TCD/V_T was observed in awake subjects. Because an increase in TCD/V_T indicates the loss of coordination between the RC and AB compartments, our findings indicate that the ability to coordinate thoracoabdominal wall motion in response to expiratory flow-resistive load is greatly disturbed in anesthetized subjects.

Two possible mechanisms might be considered with regard to the loss of coordination between the RC and AB compartments in response to expiratory loads. First, hyperinflation of the lungs due to expiratory load causes an increase in functional residual capacity (FRC). As FRC increases, the diaphragm flattens, and, as the radius of curvature increases, the diaphragm becomes less effective as a force generator. In fact, hyperinflation also causes inward motion of the RC during inspiration, an effect known as Hoover's sign (16,17). Another possible mechanism involves reflexes that serve to coordinate thoracoabdominal wall motion. Pengelly and Rebuck (18) suggested that stimulation of muscle spindles and the activation of spinal reflexes during flow-resistive and elastic loading serve to stabilize the RC during diaphragmatic contraction and to prevent paradoxical inward movement during inspiration. If these reflexes are depressed during anesthesia, the stability of the RC would be lost, augmenting inward motion of RC during inspiration. In addition, loss of stability of the chest wall may cause paradoxical movements of the thoracoabdominal wall during expiration because the contraction of abdominal muscles with severe expiratory loads is likely to induce inward motion of the abdominal wall and, at the same time, outward motion of the RC during the early expiratory phase.

These considerations, together with the observed changes in respiratory cycle and respiratory output, suggest that during expiratory flow-resistive loading, conscious efforts can play a significant role in maintaining the efficient work of breathing by actively inhibiting the increase of respiratory drive while coordinating thoracoabdominal wall motion. This suggestion is compatible with the finding that anesthetized patients in our study failed to inhibit the increase of respiratory drive and to synchronize the RC-AB wall motion. Thus, it is expected that the work of breathing under these conditions is more increased during anesthesia than it is in the conscious state. This view is also compatible with the findings that P_{ETCO_2} increased despite the increase in minute ventilation in anesthetized subjects, whereas P_{ETCO_2} did not increase despite the decrease in minute ventilation in conscious subjects during severe expiratory loading.

In conclusion, our results indicate that breathing patterns of anesthetized subjects during expiratory loading differ from those of conscious subjects. Our findings may have potentially important clinical implications in patients with asthma or chronic obstructive pulmonary disease who have obstructions to exhalation. In such patients, it is quite possible that loss of consciousness during anesthesia may cause an increase in respiratory drive with little effect on respiratory timing while blunting the ability to coordinate the thoracoabdominal wall motion, thus leading to inadequate ventilation.

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Influence of Thiopental, Etomidate, and Propofol on Regional Myocardial Function in the Normal and Acute Ischemic Heart Segment in Dogs

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DE HERT SG, VERMEYEN KM, ADRIAENSEN HF. Influence of thiopental, etomidate, and propofol on regional myocardial function in the normal and acute ischemic heart segment in dogs. Anesth Analg 1990;70:600–7.

The effects of 30-min infusions of thiopental (20, 30, 40, 50, 60, and 70 mg·kg^{-1}·h^{-1}), etomidate (2.4, 3.6, 7.2, 9.6, 12, and 14.4 mg·kg^{-1}·h^{-1}), and propofol (6, 9, 12, 15, 18, and 21 mg·kg^{-1}·h^{-1}) on regional hemodynamic variables in the normal and acute ischemic heart segment were studied in dogs using ultrasonic segment length gauges. The three agents were associated with a dose-dependent decrease in end-diastolic length, indicating a decrease in left ventricular filling. This effect was most pronounced for propofol. At the doses tested, etomidate did not significantly alter regional myocardial function. Thiopental, however, was associated with a dose-dependent decrease in systolic shortening, which was significantly greater in the ischemic segment. These findings confirm the hemodynamic stability seen with etomidate and show that thiopental depresses myocardial function more in the acute ischemic heart than in the normal heart. The decrease in systolic shortening associated with propofol was similar in the normal and in the acute ischemic heart segment.

Key Words: ANESTHETICS, INTRAVENOUS—etomidate, propofol, thiopental. HEART, ISCHEMIA.

Thiopental, etomidate, and propofol all affect the circulatory system. Whether their cardiovascular effects are due to single or combined changes in preload, afterload, or myocardial contractility is difficult to assess accurately with the classical hemodynamic monitoring tools. Consequently, some of the mechanisms responsible for the circulatory depressant effects of these agents remain controversial. Another question is whether some of these effects are different in normal and in ischemic myocardial tissue.

This study therefore posed the following questions. (a) Which mechanisms are responsible for the cardiovascular depressant effects of thiopental, etomidate, and propofol? (b) Do any of these agents depress regional ventricular function more in an ischemic than in a normal heart segment?

Methods

Experimental Procedure

Animal care conformed to national and institutional guidelines. Eighteen mongrel dogs of either sex, weighing between 20 and 32 kg (22.5 ± 4.2 kg, mean ± SD) were randomly divided into three groups of six dogs each. In group A anesthesia was induced with thiopental (20 mg/kg); group B was anesthetized with etomidate (1.5 mg/kg); and group C was anesthetized with propofol (15 mg/kg). Anesthesia was maintained during the surgical preparation with a continuous infusion of 20 mg·kg^{-1}·h^{-1} thiopental in group A, 2.4 mg·kg^{-1}·h^{-1} etomidate in group B, and 6 mg·kg^{-1}·h^{-1} propofol in group C. The trachea was intubated and constant-volume intermittent positive-pressure ventilation was instituted, delivering an oxygen-enriched air mixture (FIO_2 = 0.3). Respiratory rate and tidal volume were adjusted to maintain arterial blood gas tensions at physiological values throughout the procedure (pH: 7.35–7.45; PCO_2: 4.7–6.0 kPa [35–45 mm Hg]; PO_2: 12.0–18.6 kPa [90–140 mm Hg]). Esophageal temperature and hematocrit were also maintained within physiological limits. All

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animals received 5 $mL \cdot kg^{-1} \cdot h^{-1}$ of normal saline intravenously.

The right femoral artery was exposed and a 5F Millar micro-tip catheter (Millar Instruments, Houston, Tex.) was advanced to within 1 cm of the aortic valve for measurement of systemic arterial pressures. A left thoracotomy and pericardiotomy were performed and a second Millar micro-tip catheter was inserted via a stab wound in the apex of the left ventricle and secured in place with a purse-string suture. The micromanometer was calibrated with a mercury manometer. The second major diagonal branch of the left descending coronary artery (LAD) was dissected near its origin over a distance of about 2 cm, and a Gould electromagnetic flow probe (Gould Inc., Oxnard, Calif.) was placed around the free portion of the vessel for measurement of intracoronary flow.

Regional left ventricular length and function were assessed with pairs of ultrasonic segment length gauges (Triton Technology, San Diego, Calif.) (1,2).

One pair of crystals was implanted in the anteroapical region at the terminal end of the second diagonal branch of the LAD. The true apex was avoided because insertion of the micromanometer in the apex could influence the regional contraction pattern. A second pair of crystals was implanted in the basal region supplied by the left circumflex coronary artery. Both pairs were implanted midmyocardially, in a circumferential plane, and oriented parallel to the short axis of the left ventricle.

Baseline measurements were made after the animal had been in a steady hemodynamic state for 30 min after the completion of surgery. Using a constricting ligature, a 50% flow reduction was then created in the second diagonal branch of the LAD. Although changes in segmental wall motion induced by ischemia have been shown to occur within the first few minutes (2), a new stabilization period of 30 min was allowed before measurements were repeated.

Subsequently, the doses of the anesthetic agents were increased at intervals of 30 min: in group A, thiopental was infused at rates of 30, 40, 50, 60, and 70 $mg \cdot kg^{-1} \cdot h^{-1}$; in group B etomidate was infused at rates of 3.6, 7.2, 9.6, 12, and 14.4 $mg \cdot kg^{-1} \cdot h^{-1}$; and in group C propofol was infused at rates of 9, 12, 15, 18, and 21 $mg \cdot kg^{-1} \cdot h^{-1}$. Just before each increase in the amount of drug being infused the electrocardiogram, left ventricular pressures, aortic pressures, and segment lengths were recorded at high speed on an eight-channel recorder (Siemens Inc., Stuttgart, Federal Republic of Germany).

After the end of the experiment, the distribution of flow in the segmental coronary artery was determined by injecting methylene blue in the second diagonal branch of the LAD to assure that the piezoelectric crystals had indeed been placed in an ischemic area. The midmyocardial location of the crystals was also verified postmortem in each dog.

To evaluate the effect of time on our experimental model, we subjected, in a preliminary study, three animals in each group to the basic anesthetic technique and surgery. Hemodynamic parameters were recorded 30 min after the completion of surgery, 30 min after the 50% flow reduction in the second diagonal branch of the LAD, and again 2.5 h later.

Computations

End-diastole was determined by the peak of the R wave on the electrocardiogram. Left ventricular pressure at that moment was defined as the end-diastolic pressure and the corresponding length as the end-diastolic length (EDL). The timing of the dicrotic notch was transposed onto the left ventricular pressure tracing. The pressure at aortic valve closure was taken as end-systolic pressure and the corresponding segment length as the end-systolic length (ESL). Systolic shortening (SS) was expressed as percentage of EDL with the following formula:

$$\%SS = (EDL - ESL)/EDL \times 100.$$

Measurements were made at end expiration to prevent respiratory interference.

The results were analyzed statistically using analysis of variance for repeated measurements; where appropriate this was followed by the Scheffe F-test. To evaluate differences between the normal and the ischemic segments, measurements made after the flow reduction were taken as the reference for statistical analysis. As the baseline and start values were different for the ischemic anteroapical and the normal basal segment, comparison of absolute values was inappropriate. Therefore, the values at each measurement were subtracted from those at the start of the experiment. The results obtained in the normal and the ischemic segment were compared using paired Student's *t*-test. All differences were considered statistically significant with $P < 0.01$.

Results

Regional Myocardial Function

Baseline measurements showed SS to be significantly greater in the anteroapical region than in the basal region for the three groups.

Table 1. Systemic Hemodynamic and Regional Segmental Data for Increasing Doses of Thiopental

Thiopental	Heart rate (beats/min)	LVESP (mm Hg)	LVEDP (mm Hg)	%SS anteroapical segment	%SS basal segment	EDL anteroapical segment (mm)	EDL basal segment (mm)
Baseline (20 $mg \cdot kg^{-1} \cdot h^{-1}$)	122 ± 15	106 ± 10	7 ± 3	15.3 ± 1.9	9.6 ± 1.2	12.4 ± 0.4	11.5 ± 0.4
Start (20 $mg \cdot kg^{-1} \cdot h^{-1}$)	124 ± 17	104 ± 11	7 ± 3	11.2 ± 1.3	9.4 ± 0.9	12.8 ± 0.6	11.5 ± 0.3
30 $mg \cdot kg^{-1} \cdot h^{-1}$	116 ± 21	97 ± 8	7 ± 4	7.9 ± 1.1[a]	9.1 ± 0.6	12.6 ± 0.5	11.4 ± 0.3
40 $mg \cdot kg^{-1} \cdot h^{-1}$	108 ± 13	89 ± 12	6 ± 4	5.8 ± 0.8[a]	8.3 ± 0.7[a,b]	12.6 ± 0.3	11.3 ± 0.2
50 $mg \cdot kg^{-1} \cdot h^{-1}$	97 ± 15	80 ± 9[a]	6 ± 2	4.4 ± 0.6[a]	7.2 ± 1.0[a,b]	12.5 ± 0.2[a]	11.2 ± 0.3[a]
60 $mg \cdot kg^{-1} \cdot h^{-1}$	99 ± 23	69 ± 7[a]	5 ± 3	3.6 ± 0.8[a]	6.1 ± 0.9[a,b]	12.4 ± 0.3[a]	11.1 ± 0.2[a]
70 $mg \cdot kg^{-1} \cdot h^{-1}$	102 ± 24	61 ± 10[a]	4 ± 2	2.2 ± 0.6[a]	5.6 ± 0.8[a,b]	12.3 ± 0.2[a]	11.0 ± 0.2[a]

Values are mean ± SEM for six animals. Baseline = after stabilization following surgical preparation; start = after stabilization following 50% reduction in flow in the second diagonal branch of the left anterior descending artery. The subsequent rows show the data obtained at 30-min infusions of increasing doses of thiopental. LVESP = left ventricular end-systolic pressure; LVEDP = left ventricular end-diastolic pressure; EDL = end-diastolic length; and %SS = percentage systolic shortening.

[a] $P < 0.01$ compared with start values.

[b] $P < 0.01$ compared with values for the anteroapical segment.

The 50% flow reduction in the second diagonal branch of the LAD resulted in a significant increase in EDL and a decrease in SS of the anteroapical segment. During the isometric contraction phase a paradoxical lengthening of the segment was apparent, and during the ejection phase an early bulging appeared. The flow reduction also induced a slight postsystolic shortening.

This constant and comparable change—both quantitatively and qualitatively—in segmental contractile behavior in all animals is additional evidence that the segment length gauges were indeed placed in the ischemic segment and suggest that the 50% reduction in flow had a similar effect on changes in regional contractility in the different animals in the three groups. The reduction in flow in the second diagonal branch of the LAD had no apparent influence on the contraction pattern of the basal segment.

Thiopental (Table 1). Thiopental induced comparable dose-dependent decreases in EDL in the basal and in the ischemic anteroapical segment. There was also a significant dose-dependent decrease in SS in both segments. The decrease in SS seen with the higher doses of thiopental was significantly greater in the ischemic anteroapical segment than in the normal basal segment.

Etomidate (Table 2). Etomidate produced dose-dependent decreases in EDL in both segments. Increasing the infusion dose did not alter SS significantly in either segment.

Propofol (Table 3). Propofol induced a statistically significant dose-dependent decrease in EDL, comparable in both segments. Systolic shortening also decreased in both segments but this reached statistical significance only at higher infusion rates. This dose-dependent decrease in SS shortening was not significantly different in the two segments.

Systemic Hemodynamics

Baseline systemic hemodynamic data were similar in the three groups. The 50% reduction in flow in the second diagonal branch of the LAD and the subsequent changes in contraction pattern of the anteroapical region did not significantly affect systemic hemodynamic function. All three agents caused a statistically significant dose-dependent decrease in left ventricular end-systolic pressure. Changes in left ventricular end-diastolic pressure and heart rate were not statistically significant.

Control Study

None of the hemodynamic parameters measured in the preliminary control study (segment length data and systemic hemodynamics) changed significantly with time. Therefore, as far as the measured parameters are concerned, the effect of time on our model can be excluded.

Discussion

This study was designed to evaluate which mechanisms are responsible for the cardiovascular actions of thiopental, etomidate, and propofol. Therefore, the changes in regional myocardial hemodynamics with the three agents were compared with their

Table 2. Systemic Hemodynamic and Regional Segmental Data for Increasing Doses of Etomidate

Etomidate	Heart rate (beats/min)	LVESP (mm Hg)	LVEDP (mm Hg)	%SS anteroapical segment	%SS basal segment	EDL anteroapical segment (mm)	EDL basal segment (mm)
Baseline (2.4 mg·kg^{-1}·h^{-1})	127 ± 24	108 ± 12	7 ± 4	14.1 ± 1.1	9.8 ± 0.7	12.3 ± 0.4	11.4 ± 0.4
Start (2.4 mg·kg^{-1}·h^{-1})	122 ± 19	110 ± 14	7 ± 4	10.9 ± 1.6	9.9 ± 1.0	12.7 ± 0.5	11.4 ± 0.4
3.6 mg·kg^{-1}·h^{-1}	112 ± 22	101 ± 9	7 ± 3	10.4 ± 0.9	9.7 ± 0.9	12.7 ± 0.6	11.2 ± 0.3
7.2 mg·kg^{-1}·h^{-1}	104 ± 16	95 ± 8	7 ± 4	10.6 ± 1.0	9.8 ± 1.0	12.6 ± 0.4	11.2 ± 0.4
9.6 mg·kg^{-1}·h^{-1}	101 ± 13	86 ± 10^a	6 ± 3	10.2 ± 0.8	9.6 ± 0.8	12.5 ± 0.4	11.1 ± 0.4
12 mg·kg^{-1}·h^{-1}	98 ± 19	79 ± 11^a	6 ± 2	9.9 ± 1.2	9.9 ± 0.9	12.3 ± 0.3^a	11.0 ± 0.3^a
14.4 mg·kg^{-1}·h^{-1}	96 ± 14	71 ± 7^a	6 ± 3	10.0 ± 0.9	9.7 ± 1.0	12.3 ± 0.3^a	10.9 ± 0.3^a

Values are mean ± SEM for six animals. Baseline and start represent the same conditions as for Table 1. The subsequent rows show the data obtained at 30-min infusions of increasing doses of etomidate. Abbreviations are the same as those used in Table 1.

[a] $P < 0.01$ compared with start values.

Table 3. Systemic Hemodynamic and Regional Segmental Data for Increasing Doses of Propofol

Propofol	Heart rate (beats/min)	LVESP (mm Hg)	LVEDP (mm Hg)	%SS anteroapical segment	%SS basal segment	EDL anteroapical segment (mm)	EDL basal segment (mm)
Baseline (6 mg·kg^{-1}·h^{-1})	125 ± 22	105 ± 13	6 ± 3	14.6 ± 1.7	9.5 ± 0.9	12.0 ± 0.4	12.2 ± 0.4
Start (6 mg·kg^{-1}·h^{-1})	127 ± 29	106 ± 12	6 ± 3	11.6 ± 1.9	9.5 ± 1.1	12.4 ± 0.6	12.1 ± 0.4
9 mg·kg^{-1}·h^{-1}	116 ± 19	84 ± 16^a	5 ± 3	10.5 ± 1.2	9.3 ± 1.0	11.9 ± 0.5^a	11.5 ± 0.5^a
12 mg·kg^{-1}·h^{-1}	111 ± 16	66 ± 9^a	5 ± 2	9.2 ± 0.9	9.1 ± 0.9	11.5 ± 0.4^a	11.3 ± 0.4^a
15 mg·kg^{-1}·h^{-1}	106 ± 21	59 ± 10^a	5 ± 2	8.9 ± 1.1^a	8.7 ± 0.6^a	11.4 ± 0.4^a	11.1 ± 0.4^a
18 mg·kg^{-1}·h^{-1}	97 ± 21	52 ± 7^a	4 ± 2	8.7 ± 0.9^a	8.4 ± 1.0^a	11.3 ± 0.5^a	10.9 ± 0.5^a
21 mg·kg^{-1}·h^{-1}	100 ± 24	49 ± 8^a	3 ± 2	8.2 ± 0.7^a	8.1 ± 0.7^a	11.1 ± 0.4^a	10.7 ± 0.5^a

Values are mean ± SEM for six animals. Baseline and start represent the same conditions as for Table 1. The subsequent rows show the data obtained at 30-min infusions of increasing doses of propofol. Abbreviations are similar to those used in Table 1.

[a] $P < 0.01$ compared with start values.

effects on left ventricular end-systolic pressure. In Figure 1 it can be seen that different mechanisms underlie the negative cardiovascular effects of the three drugs. Thiopental induced a dose-dependent decrease in SS. This decrease was greater in the ischemic anteroapical segment than in the control basal segment. At the doses tested, etomidate did not alter SS significantly, whereas propofol decreased SS only at higher doses.

Although SS is currently used to assess regional myocardial performance, its value is determined not only by the intrinsic contractile state of the myocardium but also by ventricular loading conditions (3). Therefore, simultaneous evaluation of changes in EDL and SS is necessary to distinguish between effects on ventricular loading and myocardial performance. As seen in Figure 2, the cardiovascular effects of etomidate and propofol can be attributed mainly to a decrease in ventricular filling, whereas with thiopental the decrease in SS was a more important factor. Unlike what was seen with thiopental, etomidate and propofol had similar effects on the normal and acute ischemic heart segment.

Thiopental has been shown to decrease venous tone (4,5). This vasodilation results in decreased venous return, which is reflected in the decrease in EDL that we found. The increase in venous capacitance has been attributed to both a central nervous system action and a direct action on venous smooth muscle (4,5). Etomidate, on the other hand, decreases peripheral resistance. Both a decreased central nervous sympathetic stimulation and an autoregulation secondary to a decreased regional oxygen consumption have been described as causal mechanisms (6–8). Propofol induces peripheral vasodilation. Whether this vasodilation involves mainly the arteries and arterioles rather than the venous capacitance vessels still is controversial (9,10).

Of the three agents we evaluated, the effects of thiopental on myocardial contractility have been most extensively studied. From in vitro studies it appears that the reduction in developed tension by thiopental can be attributed mainly to inhibition of transsarcolemmal calcium flux (11–16). Etomidate has also been shown to have a direct negative inotropic effect, perhaps mediated by inhibition of calcium influx with

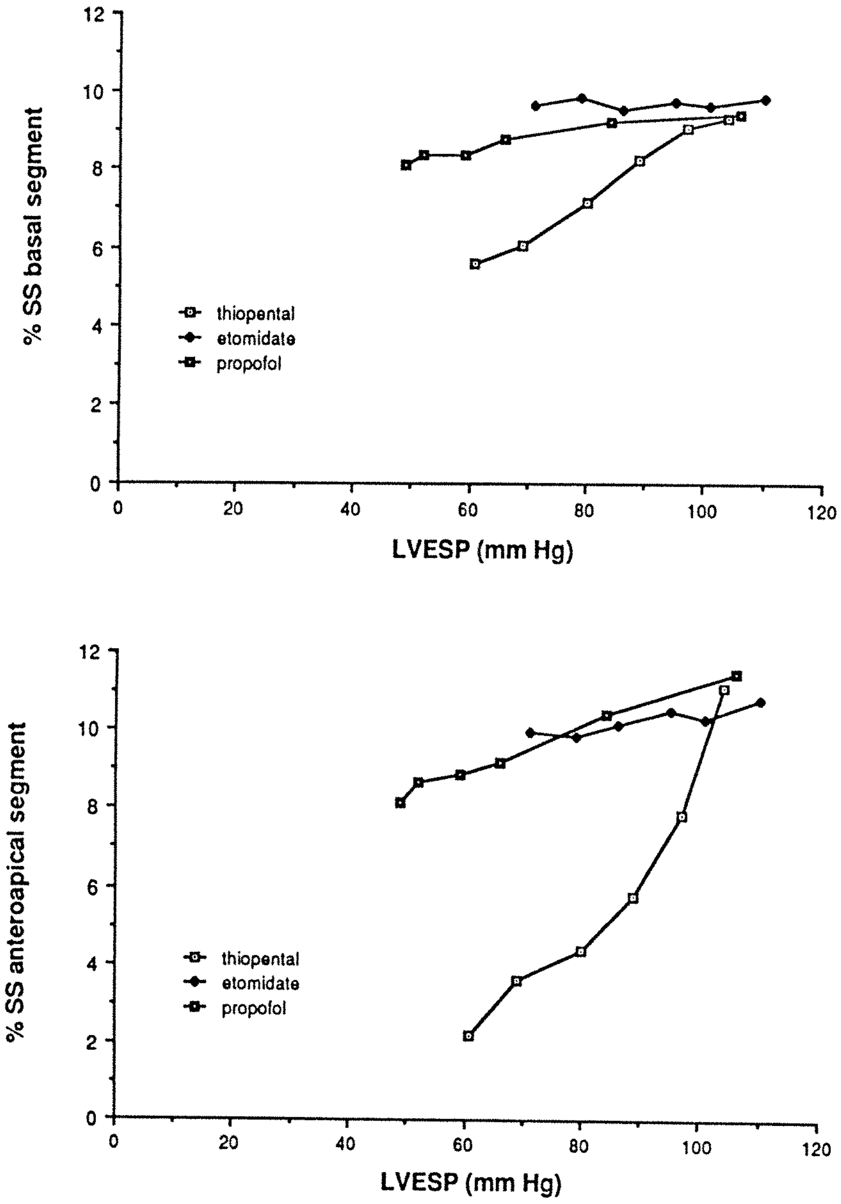

Figure 1. Changes in systolic shortening and left ventricular end-systolic pressure as a function of increasing doses of thiopental, etomidate, and propofol. Values are taken from Tables 1, 2, and 3. For the sake of clarity the bars representing 1 SEM have been omitted.

only very little effect on the availability of intracellular calcium (17). That the negative inotropic effect of etomidate is, at equianesthetic doses, half as pronounced as for thiopental (14) might explain why we found no significant change in SS for etomidate at the doses tested in this experiment.

Less is known about the negative inotropic effects of propofol. Whether the decrease in SS that we found at higher doses is a load-dependent phenomenon or is due to a central cardiovascular depression or to a direct negative inotropic effect cannot be elucidated with this model. Several studies have offered indirect evidence that propofol depresses myocardial contractility both when administered in bolus and when administered in continuous infusion (18–21). These studies, however assumed left ventricular EDP or its correlate to be a reliable index of left ventricular preload. Given the nonlinear relationship of left ventricular end-diastolic volume and left ventricular EDP, this is not necessarily true. Therefore, it cannot be excluded that some of these reported changes of myocardial function are in part load-dependent. In a recent study, Coetzee et al. (22) used the end-systolic pressure-length relationship to evaluate changes in regional myocardial contractility. As this measure has been proven to be a reliable, relatively load-independent measure of regional myocardial function (3), their results have offered more direct evidence that propofol causes a dose-related depression of myocardial contractility.

A few comments should be made regarding the interpretation of the changes of EDL and SS in this

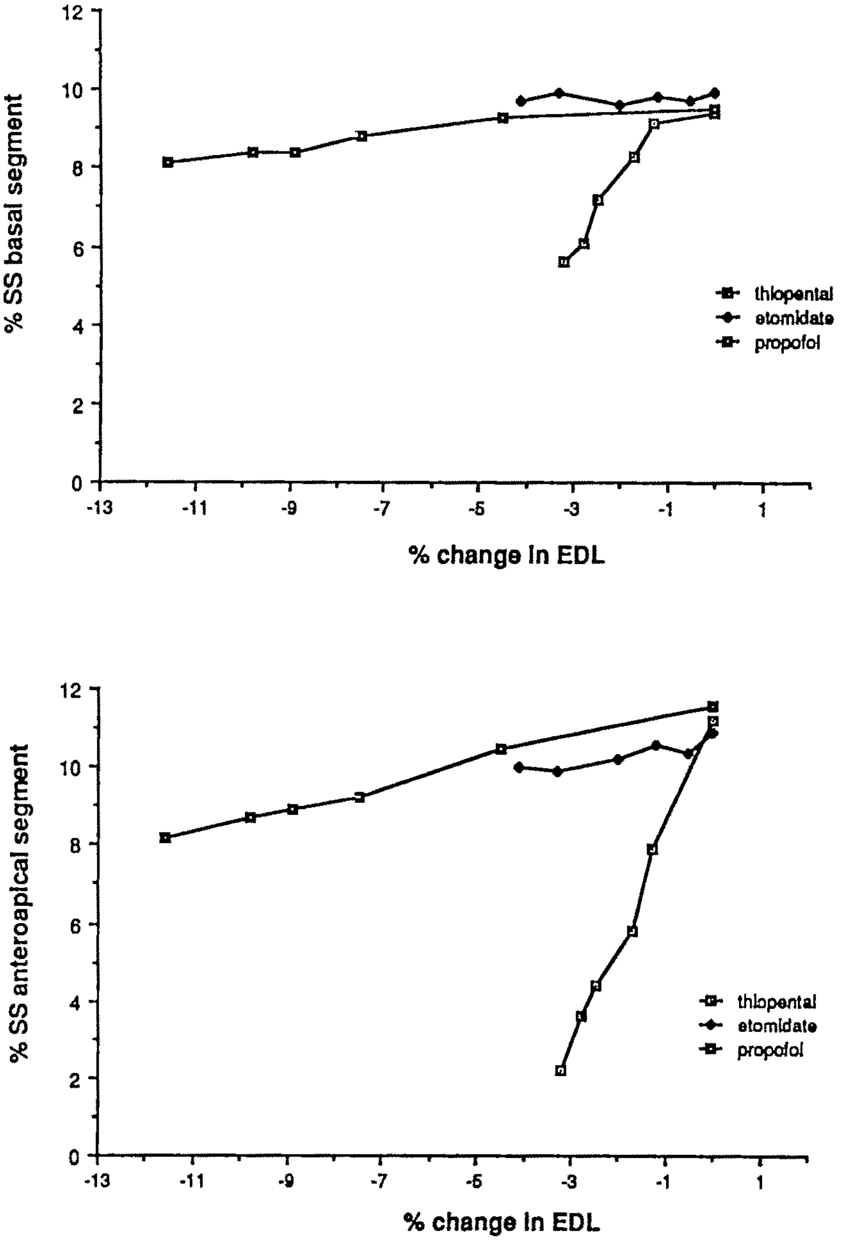

Figure 2. Changes in systolic shortening and end-diastolic length with increasing doses of thiopental, etomidate, and propofol. Values for %SS are taken from Tables 1, 2, and 3. The percent change in EDL from the starting value is calculated from the data in Tables 1, 2, and 3.

study. The decreases in EDL associated with thiopental, etomidate, and propofol were interpreted as a drug-induced and dose-dependent effect of these agents on ventricular loading. We reject the possibility that inadequate volume replacement over time was responsible for these decreases in EDL. In all animals normal saline was continuously infused at 5 mL·kg^{-1}·h^{-1}, a dose that has been reported previously as adequate for anesthetized animals undergoing thoracotomy (23). In addition, if an insufficient fluid therapy were the reason for the observed decrease in EDL, a similar change would be present in the three groups, because the duration of the experiments was the same in all animals. However, the decrease in EDL clearly differed among the three groups.

In the interpretation of the changes in SS, two aspects of the cardiac physiology should be borne in mind. First, the left ventricle has a nonhomogeneous contraction pattern, and, second, changes in ventricular loading also alter the geometry of contraction (24,25). Therefore, the difference in change in SS between the ischemic and the normal segment with thiopental is not necessarily a drug-induced effect but might be a normal physiologic response to a decreased ventricular filling. However, if either a nonhomogeneous contraction pattern or a changed geometry of contraction were the reason for the different change in SS between the two segments, a similar response would be present in the etomidate and the propofol group. Our results, on the contrary, demonstrate that, unlike thiopental, etomidate and propofol did not affect SS differently in both segments. This means that our regional SS findings with thiopental can be attributed to a drug-induced effect.

Certain aspects of the experimental protocol used in this study merit comment. Baseline measurements were obtained from animals during basal anesthesia. Although the use of unanesthetized animals as controls might be preferred, the need for elaborate measurements in this experiment would present important problems in the awake dog. For this reason we chose to do this study under the background of basal anesthesia. To prevent any problem of modification of the hemodynamic effects due to a combination of different anesthetic agents, we decided to use only one anesthetic in each of the three groups.

To avoid acute changes of the cardiovascular variables, the anesthetics were administered by continuous intravenous infusion. By increasing the infusion rate of the drugs without bolusing, it is unlikely that plasma levels of each drug had reached a steady state at the end of each 30-min period. Therefore, conclusions, based on a particular infusion rate cannot be made from this study. Following the trends with increasing infusion rates, however, allowed an evaluation of the different mechanisms underlying the cardiovascular depressant effects of thiopental, etomidate, and propofol.

In conclusion, this study confirms the hemodynamic stability of etomidate in the presence of both normal and acute ischemic myocardium. Thiopental depresses regional ventricular function more in the acute ischemic heart segment than in the normal segment. The effect of propofol on regional function, on the contrary, is similar in the normal and acute ischemic heart. Clinical extrapolation of results obtained from animal experiments, however, is associated with a number of inherent hazards. Moreover, an isolated coronary stenosis causing a single acute ischemic zone, as in this model, is probably an uncommon clinical occurrence. Therefore we believe that additional clinical and experimental studies using a chronic ischemic heart model are necessary to elucidate definitely the mechanisms involved in the hemodynamic effects of these agents.

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Comparison of Halothane, Isoflurane, Alfentanil, and Ketamine in Experimental Septic Shock

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VAN DER LINDEN P, GILBART E, ENGELMAN E, SCHMARTZ D, DE ROOD M, VINCENT J-L. Comparison of halothane, isoflurane, alfentanil, and ketamine in experimental septic shock. Anesth Analg 1990;70:608–17.

The effects of four commonly used anesthetic agents, halothane, isoflurane, alfentanil, and ketamine, on cardiovascular function and oxygen balance were studied in a dog model of septic shock. After initial pentobarbital administration, the dogs were given Escherichia coli *endotoxin (3 mg/kg) and, after 30 min, fluids to restore cardiac filling pressures to baseline levels. This resulted in a low resistance shock in all animals. Dogs were then given for 2 h either halothane (n = 9, 0.5 MAC), isoflurane (n = 9, 0.5 MAC), or alfentanil (n = 9, 150 μg/kg IV plus 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or ketamine (n = 9, 2 mg/kg IV plus 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$) or no anesthetic (control: n = 9). Mean arterial pressure increased in the control group (+11 ± 18 mm Hg) and with ketamine (+10 ± 20 mm Hg), remained unchanged with isoflurane (−2 ± 11 mm Hg), and decreased with halothane (−22 ± 23 mm Hg) and alfentanil (−9 ± 23 mm Hg). Heart rate tended to increase in the control group but decreased with the four anesthetic agents, especially with alfentanil and halothane. Cardiac index and left ventricular stroke work index increased in the control group and in each anesthetic group except the halothane group. Systemic vascular resistance decreased in all groups except in the ketamine group. In the control group, the increase in cardiac index was associated with significant increases in oxygen delivery and consumption, and with a significant decrease in blood lactate levels. There was a dramatic decrease in oxygen consumption in all anesthetic groups, whereas oxygen delivery failed to increase only with halothane. Blood lactate increased significantly with halothane (5.0 ± 1.5 to 6.3 ± 1.4 mM/L) and isoflurane (4.8 ± 1.1 to 5.3 ± 1.2 mM/L), remained unchanged with alfentanil (4.5 ± 1.5 and 4.6 ± 0.8 mM/L), and tended to decrease with ketamine (4.9 ± 1.4 to 4.5 ± 1.4 mM/L). In conclusion, among the four anesthetic agents tested, halothane had the least desirable effects. Ketamine best preserved cardiovascular function and appeared to have the least deleterious effects on the hypoxic tissues. Thus, ketamine could be the anesthetic agent of choice in septic shock.*

Key Words: ANESTHETICS, INTRAVENOUS—alfentanil, ketamine. ANESTHETICS, VOLATILE—halothane, isoflurane. SHOCK, SEPTIC—IV and inhalation anesthetics.

Septic shock is characterized by alterations of blood flow distribution associated with abnormal tissue oxygen extraction. Myocardial depression can also occur early in the course of septic shock, even when cardiac output is not depressed (1–3). In these conditions, oxygen consumption (Vo_2) can become dependent on oxygen delivery (Do_2) (4–6).

The early eradication of the septic focus producing septic shock is essential. This may require surgery under general anesthesia. The anesthetic agents used can have complex effects on both Do_2 and Vo_2. On the one hand, they can decrease Do_2 by depressing myocardial contractility and by altering vascular tone (7–13). On the other hand, they can diminish oxygen demand by reducing exogenous and endogenous stimuli. Abolishment of the work of breathing and decreased body temperature during anesthesia can contribute to reduction of oxygen requirements (14,15). However, anesthetic agents do not seem to decrease cellular metabolism below the physiologic range, and, therefore, they are not general metabolic depressants (16).

Even in the absence of severe hemodynamic impairment, anesthesia can sometimes alter the balance between oxygen supply and oxygen demand. Blood lactate levels can increase, indicating the development of anaerobic metabolism that reflects tissue hypoxia (17–20).

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Few data are available on the effects of anesthetic agents in septic shock. This information could, however, optimize the anesthetic management of the critically ill septic patient. To address this problem, we studied the effects of commonly used anesthetic agents using a canine septic shock model. In this model, endotoxin administration followed by fluid infusion in amounts determined to restore and maintain normal cardiac filling pressures results in a low-resistance type of shock, as in humans. This model has been found suitable for studying the effects of various therapeutic interventions (21–23). We studied two inhalation anesthetics, halothane and isoflurane, and two intravenous agents, ketamine and alfentanil. To maintain the reproducibility of the experiments and to avoid exogenous sympathetic stimulation that can alter the cardiovascular effects of the anesthetic agents, no surgical procedure was undertaken (24).

Methods

The study included 45 mongrel dogs (28.3 ± 4.5 kg) intubated after receiving 25 mg/kg of intravenous pentobarbital and mechanically ventilated on control mode with air (Elema 900 B, Siemens, Solna, Sweden). Respiratory rate was set at 12 breaths/min, with tidal volume adjusted to maintain Pa_{CO_2} between 35 and 40 mm Hg.

Electrodes were attached to the four limbs for heart rate monitoring. A Swan–Ganz catheter (model 93A-131-7F, Edwards Laboratories, Santa Ana, Calif.) was inserted via a jugular vein into a pulmonary artery. Two other catheters (16G8, Becton, Dickinson, Rutherford, N.J.) were inserted, one into a femoral vein for infusion of fluids and drugs and one from a femoral artery into the distal aorta for monitoring of arterial pressure and for arterial blood sampling.

Heart rate, arterial pressure, and pulmonary artery pressure were continuously recorded (model 7404, Hewlett-Packard, Palo Alto, Calif.); the zero pressure level was set at the midchest level.

Shock Model and Anesthetic Administration

After the initial baseline hemodynamic and gasometric evaluation, 3 mg/kg of *Escherichia coli* endotoxin (055B5, Difco Laboratories, Detroit, Mich.) were injected intravenously in 5 min. Dogs were then observed for 30 min before fluid resuscitation using 5% dextrose in 0.9% saline was started. Fluids were infused in amounts adequate to restore and maintain pulmonary artery balloon occluded pressure at the baseline level for the duration of the study. One hour after endotoxin administration, anesthesia was induced and maintained for 2 h. One hour after the end of anesthesia, the study was terminated and the dogs were killed.

The dogs were randomized in five groups of nine dogs each. The first group received an intravenous bolus of pentobarbital (1 $mg \cdot kg^{-1} \cdot h^{-1}$), as indicated to maintain controlled ventilation. This group with light barbiturate anesthesia was considered as a control group. Halothane and isoflurane were administered at the end-tidal concentrations of 0.5 MAC for the dog, i.e., 0.48% for halothane and 0.7% for isoflurane. This end-tidal concentration was monitored by an Emma gas monitor (Engström, Bromma, Sweden). Alfentanil was administered as a bolus dose of 150 $\mu g/kg$ followed by a continuous infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Ketamine was given as a bolus dose of 5 mg/kg followed by a continuous infusion of 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$.

Body temperature was kept constant throughout the study using a warm blanket and humidified heated gases.

Hemodynamic, Gasometric, and Blood Lactate Measurements

Heart rate (HR) and intravascular pressures, including mean arterial pressure (AP), mean pulmonary artery pressure (PAP), right atrial pressure (RAP), and pulmonary artery balloon occluded pressure (PAOP) were measured at end-expiration from the paper trace. Cardiac output (CO) was measured by the thermodilution technique (computer 9520A, Edwards Laboratories) by repeated injections of 5 mL of iced (<3°C) 5% dextrose in water. Each injection was started at the end of inspiration. Three to five measurements, with a variability of less than 10%, were averaged for each cardiac output determination.

Immediately after measurement of cardiac output, arterial and mixed venous blood samples were drawn for immediate measurement of blood gas tensions (ABL 2, Radiometer, Copenhagen, Denmark). Hemoglobin saturation was calculated by Rossing and Cain's nomogram (25). Lactate concentrations were measured enzymatically by an automated system (ACA, Du Pont Instruments, Wilmington, Del.).

Hemodynamic, gasometric, and blood lactate measurements were made before endotoxin administration (baseline), 30 min after endotoxin administration but before fluid resuscitation, 30 min after the initiation of fluid resuscitation (immediately before the

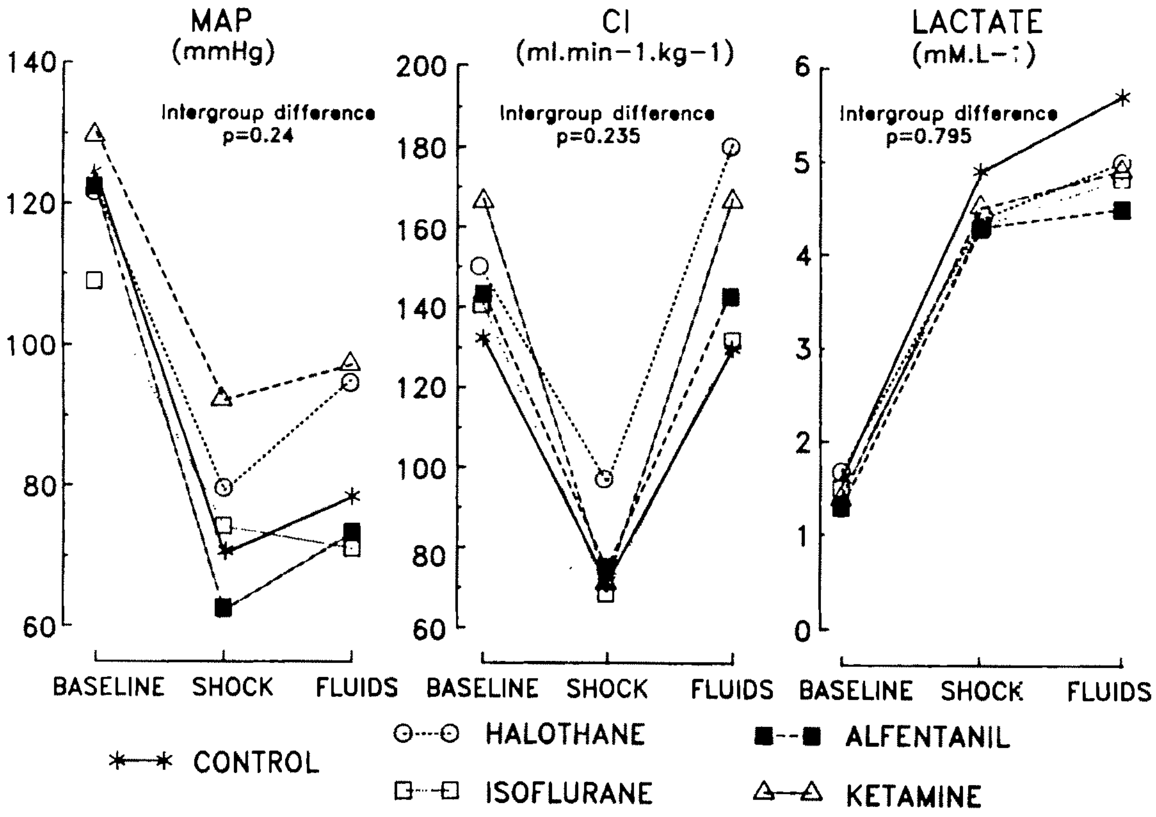

Figure 1. Mean arterial pressure, cardiac index, and blood lactate in the five groups of dogs before administration of the anesthetic agents. Baseline, before administration of endotoxin; shock, 30 min after administration of endotoxin; fluids, 30 min after infusion of 5% dextrose in 0.9% saline in amounts adequate to restore the pulmonary artery balloon occluded pressure to baseline levels.

administration of the anesthetic agent) (T_0), 60 min and 120 min after beginning the administration of the anesthetic (T_{60} and T_{120}), and 60 min after discontinuation of the anesthetic drug (T_{180}). In the control group the same timing for measurements was applied.

Cardiac index (CI), stroke index (SI), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), oxygen delivery index (Do_2), oxygen consumption index (Vo_2), and oxygen extraction (O_2 extraction) were calculated by the following formulas:

$$\text{CI (mL·min}^{-1}\text{·kg}^{-1}) = \text{CO/body weight},$$

$$\text{SI (mL·kg}^{-1}\text{·beat}^{-1}) = \text{CI/HR},$$

$$\text{LVSWI (g·m·kg}^{-1}) = (\text{AP} - \text{PAOP}) \times \text{SI} \times 0.0136,$$

$$\text{SVR (dynes·s·cm}^{-5}) = (\text{AP} - \text{RAP}) \times 79.9/\text{CO},$$

$$\text{Do}_2\ (\text{mL·min}^{-1}\text{·kg}^{-1}) = \text{CI} \times \text{Cao}_2 \times 10,$$

$$\text{Vo}_2\ (\text{mL·min}^{-1}\text{·kg}^{-1}) = \text{CI} \times (\text{Cao}_2 - \text{Cvo}_2) \times 10,$$

$$\text{O}_2 \text{ extraction (\%)} = [(\text{Cao}_2 - \text{Cvo}_2)/\text{Cao}_2] \times 100,$$

where Cao_2 and Cvo_2 represent the oxygen contents of the arterial blood and the mixed venous blood, respectively.

Statistical Analysis

The similarity of the evolution of the hemodynamic data in all groups before administration of the anesthetic agent was tested by a multivariate analysis of variance for repeated measurements, using the different groups as the grouping factor.

Intragroup statistical analysis, comparing the data at T_0, T_{60}, T_{120}, and T_{180}, was performed using Friedman two-way analysis of variance, followed by a Wilcoxon test for paired data. The α-level for each Wilcoxon test was computed as 0.05 divided by the number of performed comparisons in order to maintain an overall α-level of 0.05.

To identify intergroup differences, the differences between data obtained at T_0 and T_{120} were compared by Duncan multiple range tests. The differences between the four anesthetic groups and the control group, the differences between the two halogenated groups, and the differences between the two intravenous groups were particularly emphasized.

All values are given as mean ± SD. In all tests a

Table 1. Weight of the Dogs and Fluid Infusion in the Five Groups (Mean ± SD)

	Control (n = 9)	Halothane (n = 9)	Isoflurane (n = 9)	Alfentanil (n = 9)	Ketamine (n = 9)	Intergroup difference
Weight (kg)	28.4 ± 5.4	28.4 ± 4.7	28.6 ± 4.5	28.2 ± 4.7	27.8 ± 4.5	NS
Fluid infusion ($mL \cdot kg^{-1} \cdot h^{-1}$)						
Period 1	19.2 ± 16.1	27.5 ± 12.8	23.8 ± 10.7	24.4 ± 14.3	25.1 ± 7.5	NS
Period 2	20.3 ± 16.5	16.1 ± 8.1	19.1 ± 7.5	23.7 ± 17.8	22.0 ± 8.2	NS
Period 3	12.1 ± 11.5	11.2 ± 6.1	9.6 ± 4.2	18.1 ± 11.1	14.8 ± 7.9	NS

NS, no significant difference between the groups; period 1, initial fluid resuscitation (T_{-30}–T_0); period 2, during administration of the anesthetic agent (T_0–T_{120}); and period 3, after administration of the anesthetic agent (T_{120}–T_{180}).

Table 2. Hemodynamic Data (Mean ± SD) in the Control Group

	T_0	T_{60}	T_{120}	T_{180}
HR (beats/min)	143 ± 16	151 ± 10	152 ± 14	153 ± 10
AP (mm Hg)	77.8 ± 24.9	79.2 ± 26.7	89 ± 28	95.2 ± 27.2
PAP (mm Hg)	12.2 ± 2.1	15.1 ± 5.4	14.7 ± 6.2	14.8 ± 5.1
RAP (mm Hg)	5.0 ± 3.2	5.5 ± 3.6	5.1 ± 2.7	4.9 ± 2.6
PAOP (mm Hg)	4.8 ± 1.9	4.9 ± 2.8	5.3 ± 2.5	5.3 ± 2.5
CI ($mL \cdot min^{-1} \cdot kg^{-1}$)	129 ± 50	163 ± 68^a	169 ± 62^a	155 ± 63
SI ($mL \cdot kg^{-1} \cdot beat^{-1}$)	0.94 ± 0.49	1.08 ± 0.43	1.12 ± 0.45	1.01 ± 0.41^b
SVR ($dynes \cdot s \cdot cm^{-5}$)	1766 ± 626	1424 ± 534^a	1501 ± 449	1819 ± 559
LVSWI ($g \cdot m \cdot kg^{-1}$)	1.64 ± 0.64	2.09 ± 0.91^a	2.15 ± 0.80^a	1.99 ± 0.83
Svo_2 (%)	64.9 ± 6.6	68.9 ± 6.4	69.1 ± 4.8	68.2 ± 6.0
Do_2 ($mL \cdot min^{-1} \cdot kg^{-1}$)	22.9 ± 6.5	28.9 ± 8.3^a	30.7 ± 8.2^a	28.1 ± 9.1^b
Vo_2 ($mL \cdot min^{-1} \cdot kg^{-1}$)	5.4 ± 1.1	5.9 ± 1.4	6.4 ± 1.3^a	5.7 ± 1.6
O_2 extraction (%)	24.5 ± 5.3	21.0 ± 3.8	21.7 ± 4.4	21.5 ± 6.1
Lactate (mEq/L)	5.7 ± 1.0	5.3 ± 1.0	4.9 ± 1.17^a	4.3 ± 1.5^b

AP, arterial pressure; CI, cardiac index; Do_2, oxygen delivery index; HR, heart rate: LVSWI, left ventricular stroke work index; PAOP, pulmonary artery balloon occluded pressure; PAP, mean pulmonary artery pressure; RAP, right atrial pressure; SI, stroke index; Svo_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; Vo_2, oxygen consumption index.

T_0, before administration of the anesthetic agent; T_{60}, 60 min after the beginning of administration of the anesthetic agent; T_{120}, 120 min after the beginning of administration of the anesthetic agent; and T_{180}, 60 min after discontinuation of the anesthetic agent.

^{a}$P < 0.05$ versus before anesthesia (T_0).

^{b}$P < 0.05$ after anesthesia (T_{180}) versus during anesthesia (T_{120}).

P value less than 0.05 was considered to be statistically significant.

All statistics were performed using the software package Systat v. 3.0.

Results

In each group, endotoxin administration was associated with severe decreases in arterial pressure and cardiac index together with a significant increase in blood lactate. Initial fluid resuscitation did not significantly influence arterial pressure but restored cardiac index to baseline levels (Figure 1), systemic vascular resistance thus decreasing below baseline. This evolution was similar in all groups. The volume of fluids administered before, during, and after administration of anesthetic agents was similar in all groups (Table 1).

Intragroup Analysis

In each group, cardiac filling pressures were maintained at the baseline levels as planned (Tables 2–6).

In the control group, heart rate and arterial pressure increased only slightly, but cardiac index rose significantly (Table 2).

In the halothane group, heart rate, arterial pressure, and systemic vascular resistance decreased significantly while cardiac index remained unchanged (Table 3). When halothane was discontinued, arterial pressure and systemic vascular resistance increased. In the isoflurane group, heart rate and arterial pressure were not significantly altered (Table 4). In the alfentanil group, cardiac index increased due to an increase in stroke index despite a reduction in heart rate (Table 5). Arterial pressure and systemic vascular resistance decreased. In the ketamine group, there was no significant change in arterial pressure, cardiac

Table 3. Hemodynamic Data (Mean ± SD) in the Halothane Group

	T_0	T_{60}	T_{120}	T_{180}
HR (beats/min)	175 ± 22	157 ± 10^a	153 ± 10^a	162 ± 22
AP (mm Hg)	94.7 ± 25.2	73.9 ± 18.8^a	72.4 ± 17.3^a	100.2 ± 21.3^b
PAP (mm Hg)	13.0 ± 3.0	15.9 ± 3.5^a	15.6 ± 4.1^a	15.2 ± 3.7
RAP (mm Hg)	4.3 ± 1.7	4.6 ± 0.9	4.7 ± 0.9	4.9 ± 1.2
PAOP (mm Hg)	4.6 ± 1.4	4.7 ± 1.3	4.9 ± 1.3	4.7 ± 1.2
CI (mL·min^{-1}·kg^{-1})	182 ± 51	194 ± 29	173 ± 38	205 ± 49
SI (mL·kg^{-1}·beat^{-1})	1.06 ± 0.38	1.24 ± 0.2	1.13 ± 0.27	1.32 ± 0.51
SVR (dynes·s·cm^{-5})	1485 ± 534	1047 ± 369^a	1156 ± 356^a	1391 ± 443^b
LVSWI (g·m·kg^{-1})	2.35 ± 0.66	2.46 ± 0.38	2.19 ± 0.48	2.66 ± 0.64
Svo_2 (%)	66.9 ± 9.9	73.2 ± 5.1^a	74.6 ± 5.7^a	73.7 ± 7.5
Do_2 (mL·min^{-1}·kg^{-1})	33.9 ± 7.3	36.6 ± 5.0	33.3 ± 7.7	40.0 ± 10.1
Vo_2 (mL·min^{-1}·kg^{-1})	7.1 ± 1.0	6.4 ± 1.3	5.4 ± 1.3^a	6.5 ± 2.2^b
O_2 extraction (%)	22.1 ± 7.2	17.7 ± 4.0	16.5 ± 3.1^a	16.3 ± 2.4
Lactate (mEq/L)	5.0 ± 1.5	5.85 ± 1.2^a	6.3 ± 1.4^a	5.4 ± 1.4^b

AP, arterial pressure; CI, cardiac index; Do_2, oxygen delivery index; HR, heart rate; LVSWI, left ventricular stroke work index; PAOP, pulmonary artery balloon occluded pressure; PAP, mean pulmonary artery pressure; RAP, right atrial pressure; SI, stroke index; Svo_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; Vo_2, oxygen consumption index.

T_0, before administration of the anesthetic agent; T_{60}. 60 min after the beginning of administration of the anesthetic agent; T_{120}, 120 min after the beginning of administration of the anesthetic agent; T_{180}, 60 min after discontinuation of the anesthetic agent.

[a] $P < 0.05$ versus before anesthesia (T_0).

[b] $P < 0.05$ after anesthesia (T_{180}) versus during anesthesia (T_{120}).

Table 4. Hemodynamic Data (Mean ± SD) in the Isoflurane Group

	T_0	T_{60}	T_{120}	T_{180}
HR (beats/min)	152 ± 10	152 ± 8.9	148 ± 8.3	153 ± 6.8
AP (mm Hg)	71.4 ± 13.8	63.6 ± 17.2	69.6 ± 12.6	90.1 ± 17.9
PAP (mm Hg)	11.6 ± 3.7	13.1 ± 4.6	13.9 ± 4.2	12.7 ± 3.7
RAP (mm Hg)	5.0 ± 1.4	4.8 ± 1.6	6.2 ± 2.6	5.8 ± 1.6
PAOP (mm Hg)	4.9 ± 1.4	5.1 ± 1.6	5.3 ± 1.7	5.2 ± 1.5
CI (mL·min^{-1}·kg^{-1})	132 ± 71	170 ± 82	164 ± 65	164 ± 62
SI (mL·kg^{-1}·beat^{-1})	0.89 ± 0.52	1.12 ± 0.55	1.12 ± 0.46	1.08 ± 0.41
SVR (dynes·s·cm^{-5})	1772 ± 816	1246 ± 700^a	1272 ± 548^a	1691 ± 746^b
LVSWI (g·m·kg^{-1})	1.68 ± 0.91	2.13 ± 1.05	2.06 ± 0.81	2.11 ± 0.81
Svo_2 (%)	60.6 ± 13.1	69.4 ± 7.9^a	71.8 ± 6.4^a	67.7 ± 8.7^b
Do_2 (mL·min^{-1}·kg^{-1})	24.5 ± 12	30.1 ± 14	28.2 ± 10.8	30.2 ± 11.2
Vo_2 (mL·min^{-1}·kg^{-1})	6.3 ± 2.1	5.8 ± 2.4	5.0 ± 1.6^a	6.3 ± 2.0^b
O_2 extraction (%)	29.2 ± 12.7	20.6 ± 6.5^a	18.8 ± 5.9^a	22.0 ± 7.2^b
Lactate (mEq/L)	4.8 ± 1.1	5.3 ± 1.4^a	5.3 ± 1.2^a	4.2 ± 1.7^b

AP, arterial pressure; CI, cardiac index; Do_2, oxygen delivery index; HR, heart rate; LVSWI, left ventricular stroke work index; PAOP, pulmonary artery balloon occluded pressure; PAP, mean pulmonary artery pressure; RAP, right atrial pressure; SI, stroke index; Svo_2, mixed venous oxygen saturation; SVR, systemic vascular resistance; Vo_2, oxygen consumption index.

T_0, before administration of the anesthetic agent; T_{60}, 60 min after the beginning of administration of the anesthetic agent; T_{120}, 120 min after the beginning of administration of the anesthetic agent; and T_{180}, 60 min after discontinuation of the anesthetic agent.

[a] $P < 0.05$ versus before anesthesia (T_0).

[b] $P < 0.05$ after anesthesia (T_{180}) versus during anesthesia (T_{120}).

index, and systemic vascular resistance, but heart rate decreased (Table 6).

Intergroup Analysis

Arterial pressure increased in the control and the ketamine groups, decreased in the halothane and alfentanil groups, and was unchanged in the isoflurane group (Figure 2). Heart rate decreased with the four agents and especially with halothane and alfentanil: this evolution was significantly different from the control group, where heart rate tended to increase. Arterial pressure and heart rate also decreased more with halothane than with isoflurane. Cardiac index and left ventricular stroke work index increased in the control group and with all anesthetics except halothane. Stroke index increased in the

Table 5. Hemodynamic Data (Mean ± SD) in the Alfentanil Group

	T_0	T_{60}	T_{120}	T_{180}
HR (beats/min)	150 ± 15	133 ± 26^a	122 ± 23^a	138 ± 34^b
AP (mm Hg)	97 ± 33	80 ± 24^a	88 ± 24	99 ± 21
PAP (mm Hg)	12.8 ± 3.5	16.3 ± 4.5	17.2 ± 4.5	16.3 ± 4.7
RAP (mm Hg)	4.8 ± 1.5	4.6 ± 1.9	5.3 ± 2.0	5.7 ± 2.2
PAOP (mm Hg)	5.0 ± 1.9	4.9 ± 1.7	5.3 ± 1.5	5.0 ± 1.7
CI (mL·min^{-1}·kg^{-1})	145 ± 46	180 ± 57^a	175 ± 38^a	179 ± 44
SI (mL·kg^{-1}·beat^{-1})	0.96 ± 0.29	1.33 ± 0.45^a	1.47 ± 0.38^a	1.37 ± 0.46
SVR (dynes·s·cm^{-5})	1954 ± 650	1272 ± 423^a	1399 ± 477^a	1553 ± 436
LVSWI (g·m·kg^{-1})	1.86 ± 0.62	2.31 ± 0.8	2.24 ± 0.55	2.31 ± 0.62
Svo$_2$ (%)	66.1 ± 9.1	71.6 ± 5.2^a	71.7 ± 4.2^a	70.2 ± 4.5
Do$_2$ (mL·min^{-1}·kg^{-1})	28.7 ± 10.7	30.4 ± 7.2	29.4 ± 5.2	31.6 ± 6.5
Vo$_2$ (mL·min^{-1}·kg^{-1})	6.6 ± 1.9	5.6 ± 1.5^a	5.5 ± 0.8^a	6.3 ± 1.4^b
O$_2$ extraction (%)	24.5 ± 8.3	18.9 ± 5.3^a	18.9 ± 2.7^a	20.3 ± 4.5
Lactate (mEq/L)	4.5 ± 1.5	4.7 ± 0.7	4.6 ± 0.8	4.6 ± 1.0

AP, arterial pressure; CI, cardiac index; Do$_2$, oxygen delivery index; HR, heart rate; LVSWI, left ventricular stroke work index; PAOP, pulmonary artery balloon occluded pressure; PAP, mean pulmonary artery pressure; RAP, right atrial pressure; SI, stroke index; Svo$_2$, mixed venous oxygen saturation; SVR, systemic vascular resistance; Vo$_2$, oxygen consumption index.

T_0, before administration of the anesthetic agent; T_{60}, 60 min after the beginning of administration of the anesthetic agent; T_{120}, 120 min after the beginning of administration of the anesthetic agent; and T_{180}, 60 min after discontinuation of the anesthetic agent.

$^a P < 0.05$ versus before anesthesia (T_0).

$^b P < 0.05$ after anesthesia (T_{180}) versus during anesthesia (T_{120}).

Table 6. Hemodynamic Data (Mean ± SD) in the Ketamine Group

	T_0	T_{60}	T_{120}	T_{180}
HR (beats/min)	165 ± 17	161 ± 11	156 ± 8^a	163 ± 11^b
AP (mm Hg)	73.4 ± 14.3	74 ± 12.9	83.2 ± 10.9	89.1 ± 13.9
PAP (mm Hg)	11.8 ± 3.9	12.6 ± 3.8	12.7 ± 3.7	12.7 ± 3.2
RAP (mm Hg)	3.2 ± 2.3	3.6 ± 2.1	4.6 ± 2.6	4.2 ± 2.2
PAOP (mm Hg)	4.6 ± 2.0	4.3 ± 1.6	4.5 ± 1.8	4.6 ± 1.9
CI (mL·min^{-1}·kg^{-1})	168 ± 42	179 ± 40	187 ± 41	189 ± 44
SI (mL·kg^{-1}·beat^{-1})	1.02 ± 0.26	1.12 ± 0.28	1.20 ± 0.27	1.16 ± 0.28
SVR (dynes·s·cm^{-5})	1238 ± 181	1169 ± 175	1272 ± 323	1354 ± 265
LVSWI (g·m·kg^{-1})	2.15 ± 0.58	2.29 ± 0.53	2.42 ± 0.55	2.44 ± 0.59
Svo$_2$ (%)	62.7 ± 11.6	70.6 ± 7.3^a	70.3 ± 10^a	68.3 ± 9
Do$_2$ (mL·min^{-1}·kg^{-1})	29.9 ± 7.7	31.0 ± 7.9	31.7 ± 8.2	32.6 ± 6.1
Vo$_2$ (mL·min^{-1}·kg^{-1})	7.6 ± 1.4	5.5 ± 1.0^a	6.0 ± 1.3^a	7.3 ± 1.7
O$_2$ extraction (%)	26.8 ± 9.1	18.5 ± 3.7^a	19.7 ± 6.1^a	22.6 ± 5.3
Lactate (mEq/L)	4.9 ± 1.4	4.7 ± 1.5	4.5 ± 1.4	4.1 ± 1.3^b

AP, arterial pressure; CI, cardiac index; Do$_2$, oxygen delivery index; HR, heart rate; LVSWI, left ventricular stroke work index; PAOP, pulmonary artery balloon occluded pressure; PAP, mean pulmonary artery pressure; RAP, right atrial pressure; SI, stroke index; Svo$_2$, mixed venous oxygen saturation; SVR, systemic vascular resistance; Vo$_2$, oxygen consumption index.

T_0, before administration of the anesthetic agent; T_{60}, 60 min after the beginning of administration of the anesthetic agent; T_{120}, 120 min after the beginning of administration of the anesthetic agent; and T_{180}, 60 min after discontinuation of the anesthetic agent.

$^a P < 0.05$ versus before anesthesia (T_0).

$^b P < 0.05$ after anesthesia (T_{180}) versus during anesthesia (T_{120}).

five groups and particularly with alfentanil. Systemic vascular resistance decreased in the control group and with all agents except ketamine (Figure 2).

In the control group the increase in cardiac index was associated with significant increases in Do$_2$ and Vo$_2$ (Table 2). Do$_2$ tended to increase in all anesthetic groups except with halothane (Figure 3). In contrast to the control group, there was a dramatic decrease in Vo$_2$ in all anesthetic groups.

Blood lactate concentrations tended to decrease in the control and the ketamine groups but increased in the halothane and isoflurane groups (Figure 3). The increase in blood lactate was largest in the halothane group. Only during ketamine anesthesia did blood lactate levels decrease, although the change in lactate achieved statistical significance only 30 min after the ketamine infusion was discontinued (Table 6).

Discussion

The aim of the present study was to compare the effects of two volatile anesthetic agents, halothane

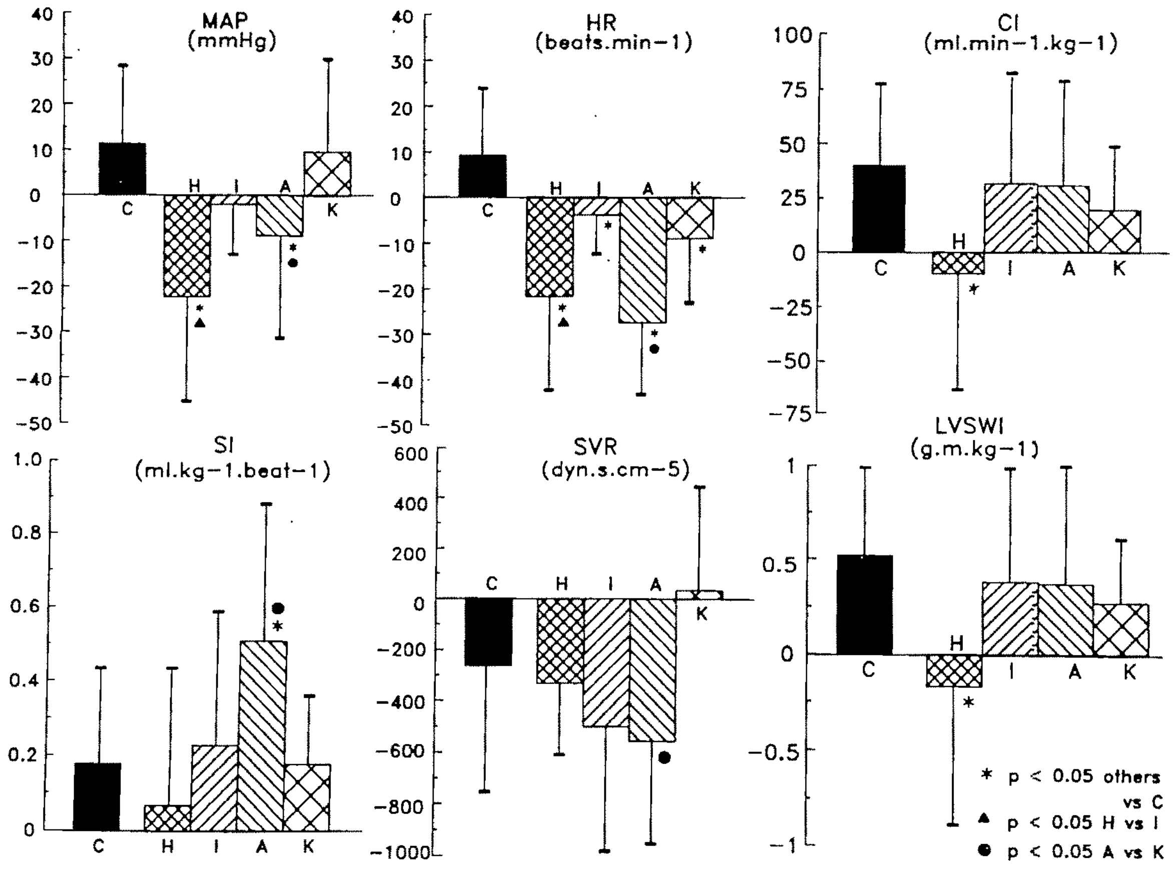

Figure 2. Intergroup comparisons of the differences between the data (mean ± SD) before and after 2 h of administration of the anesthetic agents for mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), stroke index (SI), systemic vascular resistance (SVR), and left ventricular stroke work index (LVSWI). C, control group; H, halothane group; I, isoflurane group; A, alfentanil group; K, ketamine group.

and isoflurane, and two intravenous anesthetic agents, alfentanil and ketamine, on cardiovascular and oxygen-derived parameters, on an endotoxic shock model.

The experimental model used has several limitations. First, endotoxic shock might not accurately reproduce human septic shock. However, in contrast to other studies using endotoxin, our model of fluid-resuscitated animals does not result in a low-flow state but rather in a low systemic vascular resistance, as is usually observed in patients (2,6). Recent studies in humans have also stressed the importance of endotoxin as an initiating factor in septic shock (26,27). Second, the absence of surgical operation removed the indication for administration of anesthetic agents. However, the sympathetic stimulation induced by surgery could modify the effects of anesthetic agents on both oxygen supply and oxygen demand, and we wanted to study the effects of anesthetic drugs under reproducible conditions. Third, all animals were initially treated with pentobarbital for catheter placement and mechanical ventilation. However, when administered as a single bolus injection, pentobarbital has, in dogs, only sedative effects 60–90 min after its administration (28).

Fourth, our model allows only one dose of each anesthetic agent, and the effects of anesthetics are, of course, dose dependent. In particular, the cardiovascular effects of the halogenated agents are dose dependent and enhanced in the presence of myocardial depression and/or arterial hypotension (29–31). In this study, the concentration of 0.5 MAC was chosen for halothane and isoflurane because we found it to be associated with a mean arterial pressure greater than 50 mm Hg in this dog model. The schedule for infusion of alfentanil was designed to achieve a plasma level of 100 ng/mL, which is half the plasma concentration necessary during surface surgery (32,33). These plasma concentrations, measured by radioimmunoassay in seven dogs, remained constant during the anesthetic period. They are shown in Figure 4. The protocol for infusion of ketamine was adapted from the study by Weiskopf et al. (34), who compared several anesthetic agents during graded

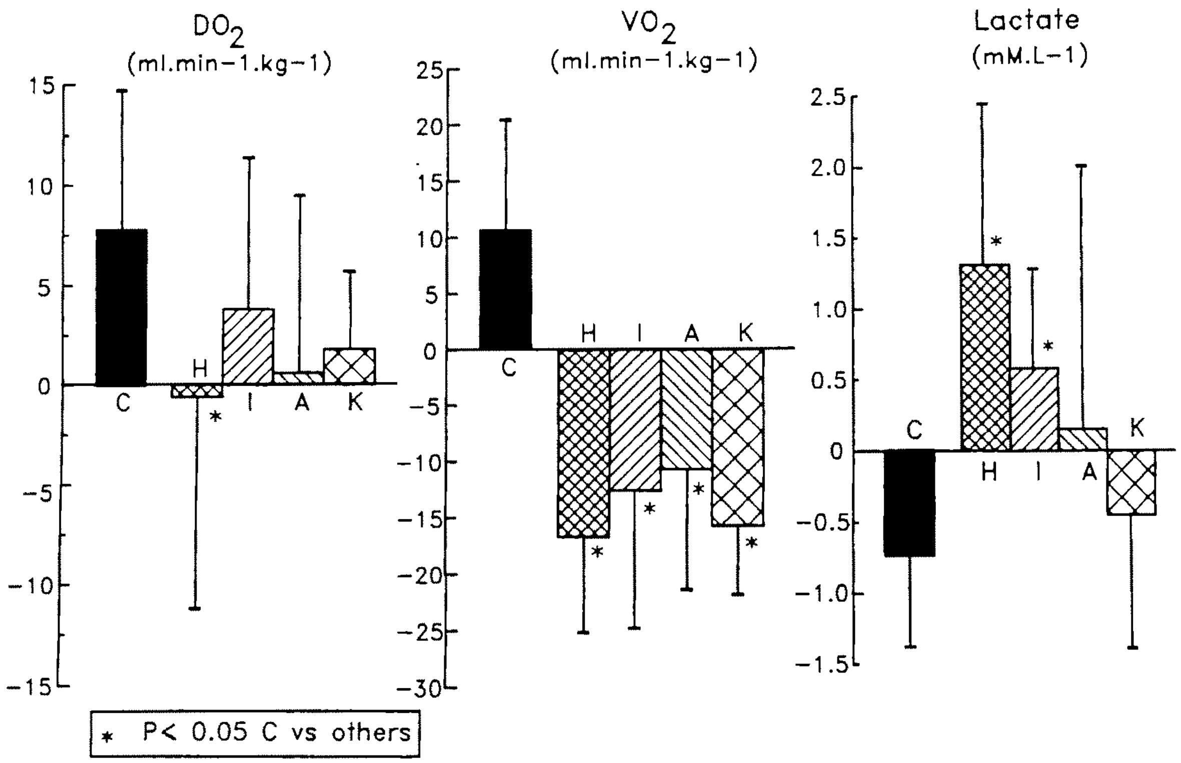

Figure 3. Intergroup comparisons of the differences between the data (mean ± SD) before and after 2 h of administration of the anesthetic agents for oxygen delivery (Do_2), oxygen consumption (Vo_2), and blood lactate. C, control group; H, halothane group; I, isoflurane group; A, alfentanil group; K, ketamine group.

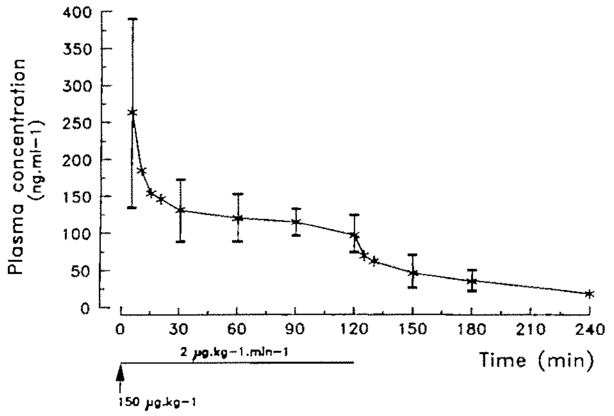

Figure 4. Alfentanil plasma levels (mean ± SD) determined by radioimmunoassay in seven dogs. The last measurement (time = 240 min) was performed in two dogs only.

hemorrhage; it was the smallest dose of ketamine necessary to prevent movement in the dog. Thus the doses of each anesthetic agent were moderate, as they might be used during anesthesia in septic shock patients. However, one cannot state that the levels of anesthesia obtained with the volatile and the intravenous agents were absolutely and entirely equal.

Of the volatile agents, halothane had the more depressant effects on arterial pressure, cardiac index, and left ventricular stroke work. As these changes occurred in the presence of constant filling pressures, they indicate that left ventricular function was altered with halothane. Cardiac function was better preserved with isoflurane and these observations are consistent with the results of previous studies (7,35).

In the alfentanil group, despite a decrease in heart rate, there was an increase in cardiac index associated with a further decrease in systemic vascular resistance. These effects are consistent with the vasodilating and also the vagomimetic properties of alfentanil (36).

With ketamine, hemodynamic function was better maintained than with the other anesthetic agents and was almost comparable to the control group. In particular, neither arterial pressure nor systemic vascular resistance was reduced. These effects could be related to the sympathomimetic actions of ketamine, which are mediated by a direct stimulation of central nervous system structures (37).

Only a few studies have compared the effects of anesthetic agents during septic shock. Most of them assessed the influence of the anesthetic technique on the natural evolution of the experimental sepsis. Schaefer et al. (38) compared enflurane, isoflurane, pentobarbital, and ketamine during endotoxic shock in rats in an attempt to reproduce the hemodynamic conditions in awake animals. They showed that isoflurane had the fewest hemodynamic effects. However, attention was not paid to the balance between Do_2 and oxygen demand. In endotoxemic pigs, Modig (39) found that mean arterial pressure and oxygen delivery were greater during anesthesia with ketamine than with metomidate (an experimental analogue of etomidate). Moreover, 6-h survival was significantly higher in the ketamine than in the metomidate group. In a porcine model of *Pseudomonas aeruginosa* septicemia, Worek et al. (40) compared ketamine and pentobarbital anesthesia to the awake state. They found that pentobarbital had profound effects on hemodynamics and survival time. In contrast, ketamine had minimal cardiodepressant effects and did not affect survival time.

We also examined the relations between Do_2, Vo_2, and oxygen demand. Blood lactate levels were used to assess the relationship between oxygen demand and Do_2. When Vo_2 decreased, an increase in blood lactate levels in the presence of a preserved or even increased Do_2 suggested that Vo_2 was reduced beyond O_2 demand, so that tissue hypoxia occurred. A potential limitation is that lactate levels can be influenced not only by increased lactate production due to anaerobic metabolism but also by decreased lactate elimination due to circulatory impairment. The anesthetic agents could interfere with lactate metabolism especially by alteration of hepatic blood flow. However, these effects are dose-dependent, so they should be limited with the relatively low dose used (41,42).

At the doses used in this study, Vo_2 decreased significantly and similarly with the four anesthetic agents. Only halothane prevented the increase in Do_2 observed in the control group. Concurrently, blood lactate levels increased during halothane anesthesia, suggesting a worsening of tissue hypoxia with this agent. During isoflurane anesthesia, cardiac function was better preserved as indicated by cardiac output and left ventricular stroke work index. However, blood lactate levels also increased, suggesting that tissue oxygenation was not better preserved with isoflurane than with halothane. The vasodilating properties of isoflurane (35) might have contributed to an O_2 extraction defect. With alfentanil, blood lactate was unaltered, suggesting that hypoxia was not profound despite further vasodilation. Blood lactate levels tended to decrease only during ketamine administration, suggesting a better balance between Do_2 and Vo_2. These results are consistent with the favorable effects of ketamine on survival observed in two previous studies on experimental septic shock (39,40).

In the control group the increase in Do_2 following fluid infusion was associated with an increase in Vo_2 and also a decrease in blood lactate levels. These results tend to support the concept that, in septic shock, an increase in Do_2 can be associated with improvement in tissue oxygenation and correction of anaerobic metabolism (5,6). Carroll and Snyder (43) also demonstrated recently in the cynomolgus monkey under ketamine anesthesia that the depressed Vo_2 due to sepsis can be reversed when Do_2 is increased.

In conclusion, among the four anesthetic agents tested on this dog model, halothane had the least desirable effects during endotoxic shock; ketamine best preserved cardiovascular function and appeared to have the least deleterious effect on the hypoxic tissues. These data suggest that ketamine could be the anesthetic agent of choice in septic shock.

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1990;70:618–23

Effects of Isoflurane on Conduction Velocity and Maximum Rate of Rise of Action Potential Upstroke in Guinea Pig Papillary Muscles

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OZAKI S, NAKAYA H, GOTOH Y, AZUMA M, KEMMOTSU O, KANNO M. Effects of isoflurane on conduction velocity and maximum rate of rise of action potential upstroke in guinea pig papillary muscles. Anesth Analg 1990;70:618–23.

This study was undertaken to determine whether isoflurane, a volatile anesthetic that is reported to possess a wide margin of cardiovascular safety, exerts electrophysiological effects on cardiac tissue. By use of standard microelectrode techniques, effects of isoflurane on the maximum rate of rise of action potential upstroke ($\dot{V}_{max}$) and conduction velocity were examined in guinea pig papillary muscles. Isoflurane decreased action potential amplitude and action potential duration in a concentration-dependent fashion. Isoflurane at 1.5 and 2.0 MAC decreased conduction velocity with as little influence on the maximum rate of rise of action potential upstroke as that exerted by halothane and enflurane. However, the effect of isoflurane in slowing intraventricular conduction was less than that of halothane and enflurane when compared at equi-MAC concentrations. Thus, isoflurane may be a safer anesthetic for the patients with intraventricular conduction abnormalities.

Key Words: ANESTHETICS, VOLATILE—isoflurane. HEART, CONDUCTION—isoflurane.

Knowledge of the effects of volatile anesthetics on cardiac conduction is important in the management of patients with heart block and other cardiac rhythm disorders during anesthesia. It has been recognized that halothane and enflurane slow the discharge of the sinoatrial node and the conduction of the atrioventricular node (1–7). In addition, these anesthetics sensitize the heart to catecholamines and cause ventricular tachyarrhythmias in the presence of adrenergic agonists (8–10). In contrast to halothane and enflurane, isoflurane has been found to exert little inhibitory action on cardiac conduction (11). Data from animal studies also suggest that isoflurane does not increase epinephrine-induced arrhythmogenicity (12). Thus it has been suggested that isoflurane may be the inhalation anesthetic of choice for patients with preexisting myocardial electrical instability.

We previously reported that halothane and enflurane impair not only the atrioventricular conduction but also intraventricular conduction (7). Our recent study using conventional microelectrode techniques (13) has suggested that these volatile anesthetics impair the intraventricular conduction by mechanism(s) different from those involving fast sodium channel blockers such as lidocaine or tetrodotoxin. Both halothane and enflurane decrease conduction velocity with little influence on the maximum rate of rise of action potential upstroke ($\dot{V}_{max}$), whereas fast channel blockers (i.e., tetrodotoxin and lidocaine) decrease the square of the conduction velocity in proportion to the decrease in $\dot{V}_{max}$ (13). These findings suggest that these volatile anesthetics might slow conduction, presumably by increasing the internal longitudinal resistance (i.e., by impairing cell-to-cell electrical coupling). These considerations prompted us to examine the effects of isoflurane, another volatile anesthetic that reportedly has little electrophysiologic effect on cardiac tissue (11,12), on $\dot{V}_{max}$, and conduction velocity of excitation in guinea pig papillary muscles. The findings presented here indicate that isoflurane also slows the intraventricular conduction without affecting $\dot{V}_{max}$, although the slowing effect on the conduction is less marked than the effect of halothane or enflurane.

Methods

This study was approved by the Animal Research Committee of Hokkaido University School of Medi-

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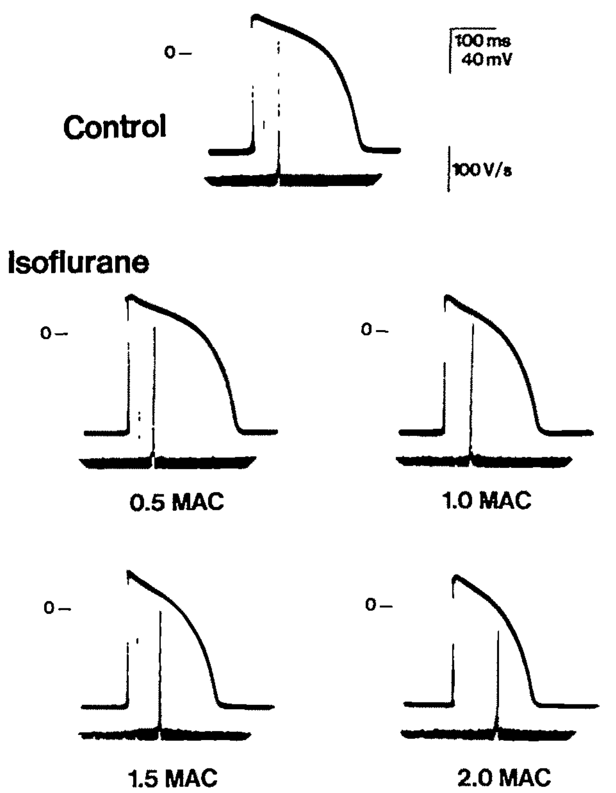

Figure 1. Effects of isoflurane on the action potential and on $\dot{V}_{max}$ in guinea pig papillary muscles driven at 1.0 Hz. A control action potential is shown in the upper panel; the action potentials recorded 20 min after 0.5 MAC, 1.0 MAC, 1.5 MAC, and 2.0 MAC isoflurane are in the middle and lower panels. In each recording the upper and lower tracings indicate the transmembrane potential and dV/dt (the first time derivative of the action potential) on expanded time base, respectively. The peak value of dV/dt is $\dot{V}_{max}$. A zero millivolt level is indicated on the left side of each panel (0). Calibrations in the control record are applicable to the other records. Note that isoflurane shortened action potential duration in a concentration-dependent manner with little effect on $\dot{V}_{max}$.

cine. Guinea pigs of either sex, weighing 250–400 g, were stunned with a blow on the head and the hearts quickly removed. Each heart was immersed in an oxygenated Tyrode's solution, and papillary muscles less than 1 mm in diameter were dissected from the right ventricle. The preparations were pinned to the bottom of a 5-mL tissue chamber and continuously superfused with the modified Tyrode's solution equilibrated with 95% O_2 and 5% CO_2. The composition of the solution was as follows (mM): NaCl, 125; KCl, 4; $NaHCO_3$, 25; NaH_2PO_4, 1.8; $MgCl_2$, 0.5; $CaCl_2$, 2.7; and glucose, 5.5. The temperature of the tissue bath was maintained at 33.0° ± 1.0°C.

The preparations were stimulated at a rate of 1.0 Hz using a bipolar electrode at the cut end. Stimuli were rectangular pulses of 1-ms duration at twice the diastolic threshold, delivered from an electronic stimulator (Nihon Koden, SS-302J). Two separate microelectrode impalements were made in a line along the long axis of the preparation. Transmembrane potentials were recorded from both microelectrodes filled with 3 M KCl, which had a tip resistance of 10–30 MΩ. The microelectrodes were coupled with an Ag-AgCl junction and connected to the input stage of a high-impedance amplifier (W-P Instruments, FD 223) equipped with input capacity neutralization units (W-P Instruments, FC-23). An agar bridge containing 3 M KCl was used as a common reference electrode. Electronic differentiators with a linear output from 50 to 1000 V/s were used for measuring the maximum rate of rise of action potentials. These amplified signals were displayed on a dual-beam oscilloscope (Nihon Koden VC-9), photographed on 35-mm film, and recorded on a chart recorder (Watanabe Sokki, WR3101).

Conduction time was defined as the time between the peaks of the differentiated upstroke signals. Using a stereomicroscope with a calibrated ocular grid (Olympus SZ), the distance between the electrodes was measured with accuracy in a range of ±0.05 mm, and the conduction velocity was calculated by dividing the interelectrode distance by the conduction time. After an equilibration period of 120 min, control recordings were made and the preparations were exposed to a solution containing the lowest concentration of isoflurane. The concentration was increased stepwise at an interval of 20 min, and the recordings of action potentials were repeated. Isoflurane (Abbott, Chicago, Ill.) was introduced into the oxygen-carbon dioxide mixture through Isoflurane Vapor 19.1 (Drägerwerk AG, Lübeck, Federal Republic of Germany). The vaporizer setting used to administer 1 MAC of isoflurane was 1.28%. The actual concentration of isoflurane in the bath medium was determined by gas chromatography (Shimadsu Gas Chromatograph GG-4A PTF). Only results of experiments in which both impalements were maintained throughout are presented here; the others were discarded.

All data are presented as mean ± SEM. Statistical analyses of changes of action potential parameters and conduction velocity were performed using Student's *t*-test for paired and unpaired samples. Statistical significance was established when the probability value was <0.05. The correlation coefficients and regression equations were calculated by least-squares analysis.

Results

Concentrations of isoflurane in the superfusate, determined by gas chromatography, were 8.5 ± 0.3

Table 1. Effects of Isoflurane on Action Potential Parameters of Guinea Pig Papillary Muscles

	RMP (−mV)	APA (mV)	APD_{20} (ms)	APD_{50} (ms)	APD_{90} (ms)	$\dot{V}_{max}$ (V/s)	CV (m/s)
Control	92 ± 0	132.4 ± 1.7	157 ± 11.2	243 ± 18.6	288 ± 16.4	235 ± 34.8	0.682 ± 0.18
0.5 MAC	92 ± 0.3	130.8 ± 1.3[a]	150 ± 13.5	235 ± 20.1	275 ± 22.1	233 ± 35.4	0.669 ± 0.18
1.0 MAC	92 ± 0.4	132.4 ± 0.9	136 ± 13.5[a]	225 ± 18.5[a]	264 ± 21.4[a]	238 ± 35.8	0.657 ± 0.19
1.5 MAC	92 ± 1.1	129.2 ± 1.3[a]	125 ± 8.2[a]	212 ± 13.2[a]	249 ± 14.3[a]	228 ± 29.6	0.464 ± 0.07[a]
2.0 MAC	92 ± 0.6	124.4 ± 0.7[a]	103 ± 9.8[a]	182 ± 10.0[a]	219 ± 10.4[a]	229 ± 27.9	0.250 ± 0.04[a]

Values are expressed as mean ± SEM of five preparations.

RMP, resting membrane potential; APA, action potential amplitude; APD_{20}, action potential duration at 20% repolarization; APD_{50}, action potential duration at 50% repolarization; APD_{90}, action potential duration at 90% repolarization; $\dot{V}_{max}$, maximum rate of rise of action potential upstroke; CV, conduction velocity.

[a] $P < 0.05$ from the control value by paired *t*-test.

mg/dL at the 1.0 MAC setting and 15.9 ± 0.3 mg/dL at the 2.0 MAC setting.

Figure 1 illustrates, the typical effects of isoflurane on the action potential configuration and $\dot{V}_{max}$ in a preparation constantly driven at 1.0 Hz. These action potentials were obtained from the proximal recording site, close to the bipolar stimulation electrode. Isoflurane decreased the action potential amplitude (APA) and action potential duration (APD) in a concentration-dependent manner, without affecting resting membrane potential (RMP). In this preparation, $\dot{V}_{max}$ was barely affected by this anesthetic in concentrations up to 1.5 MAC, but slightly decreased at 2.0 MAC.

The data obtained from five preparations are summarized in Table 1. Although APAs and APDs were decreased by isoflurane in a concentration-dependent fashion, $\dot{V}_{max}$ was unaffected by the anesthetic in the concentrations examined. However, conduction velocity was significantly decreased by 1.5 and 2.0 MAC of isoflurane. These changes in action potential configuration and conduction velocity reverted toward the control after a washout period of 20 min.

A representative example of changes in $\dot{V}_{max}$ and conduction velocity produced by isoflurane at a constant stimulation frequency of 1.0 Hz is illustrated in Figure 2. Although isoflurane produced little effect on the conduction velocity in concentrations less than 1.5 MAC, 2.0 MAC of the anesthetic decreased the conduction velocity by half. However, $\dot{V}_{max}$ obtained from the distal recording site was unchanged, whereas that obtained from the proximal recording site was increased rather than decreased. Conduction velocity and $\dot{V}_{max}$ were normalized to the respective values obtained under control conditions. The control values of these parameters were assumed to be 1.0, and the values after various concentrations of isoflurane were divided by the respective control value. Then the square of conduction velocity and $\dot{V}_{max}$ were plotted on the abscissa and the ordinate, respectively, as shown in Figure 3. The solid line represents the relation that would be obtained if the decrease in $\dot{V}_{max}$ were proportional to the decrease in the square of conduction velocity. Thus, a high concentration of isoflurane decreased conduction velocity without a proportional decrease in $\dot{V}_{max}$.

The relations between the normalized $\dot{V}_{max}$ and the normalized square of the conduction velocity, which were obtained from all preparations exposed to isoflurane, are demonstrated in Figure 4. Isoflurane decreased conduction velocity disproportionately to the change in $\dot{V}_{max}$. Least-squares analyses gave the slopes of 0.04 ± 0.02. The slope values were far from the theoretical value of 1.0, which would be obtained if the square of the conduction velocity were decreased in proportion to the decrease in the $\dot{V}_{max}$ as is the case by fast sodium channel blockers such as lidocaine (13).

Effects of various concentrations of isoflurane on conduction velocity are summarized and compared with those of halothane and enflurane, which were reported in our previous study (13), in Table 2. All these volatile anesthetics decreased conduction velocity in guinea pig papillary muscles in a concentration-dependent way. However, the decrease in conduction velocity after isoflurane was significantly less than decreases after halothane or enflurane when compared at 1.5 and 2.0 MAC levels ($P < 0.05$).

Discussion

In fast-response fibers, such as Purkinje fibers, and in atrial and ventricular muscles, the rapid sodium current plays an important role in the propagation of excitation (14). According to one-dimensional cable theory, a decrease in conduction velocity is usually accompanied by a decrease in $\dot{V}_{max}$ unless internal longitudinal resistance and/or membrane capacitance are altered (15,16). Buchanan et al. (17) have reported

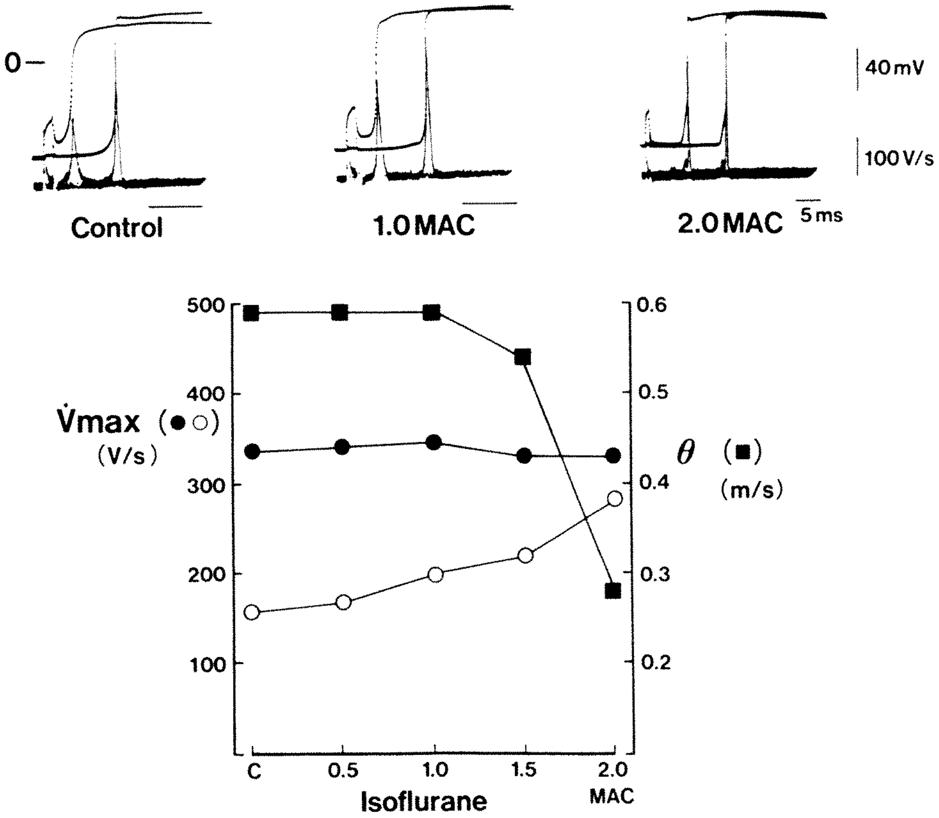

Figure 2. Effects of isoflurane on interelectrode conduction velocity and $\dot{V}_{max}$ in guinea pig papillary muscles. Upstroke of two action potentials (upper tracings) and dV/dt (the first time derivative of the action potential, lower tracings) before (control) and during 1.0 and 2.0 MAC isoflurane are shown in upper panels. Action potentials and dV/dt were recorded at a sweep speed so fast that only the initial part of action potentials is shown. A time scale of 5 ms is indicated at the bottom of each panel. A zero millivolt level is indicated on the left side. Changes of $\dot{V}_{max}$ (*open* and *closed circles*) and interelectrode conduction velocity (θ, *closed squares*) in this experiment are depicted in the lower panel. *Open* and *closed circles* indicate the $\dot{V}_{max}$ values of action potentials obtained from the proximal and distal recording sites, respectively. $\dot{V}_{max}$ and θ are on the ordinate; the concentrations of isoflurane are on the abscissa. C indicates control. Note that isoflurane at 1.5 and 2.0 MAC decreased conduction velocity without decreasing $\dot{V}_{max}$.

that fast sodium channel blockers produce a decrease in the square of the conduction velocity, a decrease proportional to the decrease in $\dot{V}_{max}$. Consistent with their report, we also observed that lidocaine and tetrodotoxin decreased conduction velocity in a way that paralleled the decrease in $\dot{V}_{max}$ in guinea pig papillary muscles (13). Halothane and enflurane, however, decreased conduction velocity with little influence on $\dot{V}_{max}$. The present study revealed both that high concentrations of isoflurane also decrease conduction velocity without affecting $\dot{V}_{max}$, and that the electrophysiologic action of isoflurane is qualitatively similar to that of halothane and enflurane.

The slowing effect of isoflurane might stem from the alterations of cable properties, probably an increase in the internal longitudinal resistance. Support for this concept derives from a recent study in which both isoflurane and halothane were reported to cause electrical uncouplings in cell pairs isolated from guinea pig ventricular muscle (18). It may be of interest to ask how these volatile anesthetics inhibit cell-to-cell coupling. Recently, Niggli et al. (19) reported that not only halothane but also aliphatic alcohols (e.g., heptanol and octanol) inhibit the Ca^{2+} inward current, the outward K^+ currents, and gap junctional conductance in guinea pig ventricular cells. They speculated that the aliphatic alcohols and inhalation anesthetics, both of which are polar molecules exhibiting pronounced surface activity, may be incorporated into the lipophilic aspect of cell membrane and cause an expansion of the membrane surface, leading to the inhibition of the ion channel function. Whatever the mechanism(s) involved, volatile anesthetics decrease conduction velocity, probably via an increase in gap junctional resistance.

It is widely held that isoflurane possesses a wider margin of safety in cardiovascular actions than halothane or enflurane (20,21). Although the nega-

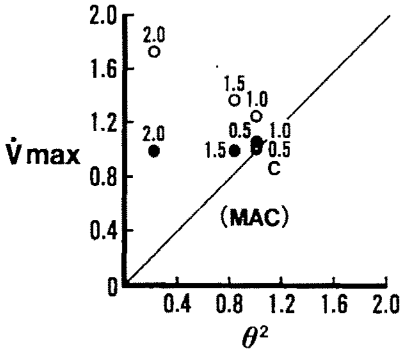

Figure 3. Effects of isoflurane on $\dot{V}_{max}$ and conduction velocity. The panel shows plots of the data from the experiment presented in Figure 2. In this panel, the data are normalized to control conduction, and $\dot{V}_{max}$ (ordinate) is plotted against the square of conduction velocity (abscissa). These values under control conditions are assumed to be 1.0. *Open* and *closed circles* indicate $\dot{V}_{max}$ values of two action potentials recorded from different cells. Concentrations of isoflurane are shown in this figure as MAC. The *solid line* represents the relationship that would be obtained if the decrease in $\dot{V}_{max}$ were proportional to the decrease in the square of the conduction velocity. Note that the square of the conduction velocity was decreased by isoflurane in a concentration-dependent manner although the $\dot{V}_{max}$ was unchanged or increased.

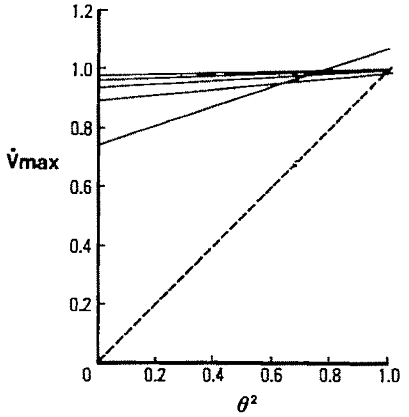

Figure 4. Relationships between changes in $\dot{V}_{max}$ (ordinate) and decreases in the square of the conduction velocity (abscissa) in preparations exposed to isoflurane ($n = 5$). In each experiment, linear regression analysis gave a straight line (sloping solid line), and all data, including the representative examples shown in Figure 3, are demonstrated. The *broken line* represents the relationship that would be obtained if the decrease in $\dot{V}_{max}$ were proportional to the decrease in the square of the conduction velocity (i.e., slope value = 1). Note that conduction velocity was decreased disproportionately to the change in $\dot{V}_{max}$.

Table 2. Effects of Isoflurane, Enflurane, and Halothane on Conduction Velocity

	Conduction velocity (% of control)			
	0.5 MAC	1.0 MAC	1.5 MAC	2.0 MAC
Isoflurane ($n = 5$)	96.9 ± 3.0	94.5 ± 5.5	74.5 ± 9.1[a,b]	44.5 ± 10.6[a,b]
Enflurane[c] ($n = 5$)	98.6 ± 0.6	86.7 ± 5.9[a]	38.2 ± 8.2[a]	15.0 ± 5.6[a]
Halothane[c] ($n = 6$)	94.8 ± 3.3	81.9 ± 8.4[a]	46.9 ± 11.1[a]	20.5 ± 4.6[a]

Values are expressed as mean ± SEM.

[a] $P < 0.05$ from the control value by paired *t*-test.

[b] $P < 0.05$ from enflurane and halothane at the same MAC level.

[c] The data of enflurane and halothane were adapted from our previous report (13).

tive inotropic effect of isoflurane is comparable to that of halothane in isolated cardiac preparations (22–24), the myocardial depressant effect of isoflurane appears to be less in intact animals and humans (25–27). In addition, isoflurane does not sensitize the heart to the arrhythmogenic effects of epinephrine, which makes it clearly different from halothane (12,28). It also has been reported that isoflurane causes little slowing of atrioventricular conduction in dogs (11). In the present study, isoflurane, like halothane and enflurane, decreased conduction velocity in the ventricular myocardium at its high concentrations. However, the magnitude of decrease in conduction velocity produced by isoflurane was significantly less than that produced by halothane and enflurane when compared at equi-MAC concentrations. Therefore, isoflurane anesthesia may be safer for patients with a risk of intraventricular conduction disturbances than halothane or enflurane.

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Dexmedetomidine, an α_2-Adrenergic Agonist, Decreases Cerebral Blood Flow in the Isoflurane-Anesthetized Dog

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ZORNOW MH, FLEISCHER JE, SCHELLER MS, NAKAKIMURA K, DRUMMOND JC. Dexmedetomidine, an α_2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. Anesth Analg 1990;70:624–30.

The purpose of this study was to examine the effects of dexmedetomidine, an α_2-adrenergic agonist, on cerebral blood flow and metabolic rate in dogs anesthetized with 0.64% isoflurane. After intubation and institution of mechanical ventilation, arterial, venous, pulmonary artery, and sagittal sinus catheters were inserted. Measurements of cerebral blood flow (CBF), cerebral metabolic rate for oxygen ($CMRO_2$), mean arterial pressure, cardiac output, and blood gas tensions were made at various levels of isoflurane anesthesia (0.64%, 1.9%, and 2.8%), after the administration of 10 μg/kg of dexmedetomidine (a dose that has been shown to reduce anesthetic requirements in dogs by >90%) and finally after 0.3 mg/kg of the α_2-adrenergic antagonist idazoxan. Despite an increase in arterial pressure, dexmedetomidine caused a marked reduction (>45%, $P < 0.05$) in CBF when compared with all preceding concentrations of isoflurane. The administration of dexmedetomidine had no effect on the $CMRO_2$. The electroencephalogram showed a loss of high-frequency activity in a pattern similar to that seen with 1.90% isoflurane. Administration of dexmedetomidine was associated with a 57% decrease in cardiac output (to 0.89 L/min). Administration of idazoxan (an α_2-adrenergic antagonist) resulted in an increase in cardiac output and a reversal of the electroencephalogram effects. This experiment indicates that 10 μg/kg of dexmedetomidine in isoflurane-anesthetized dogs is associated with a profound decrease in CBF and cardiac output in the face of an unaltered $CMRO_2$. Despite the large reduction in the $CBF/CMRO_2$ ratio, there was no evidence of global cerebral ischemia.

Key Words: BRAIN, BLOOD FLOW—dexmedetomidine. BRAIN, METABOLISM—dexmedetomidine. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—dexmedetomidine.

There has recently been substantial interest in the anesthetic properties of a class of drugs known as α_2-adrenergic agonists. α_2-Adrenergic receptors are present in the central nervous system and may be found in both presynaptic and postsynaptic locations (1,2). α_2-Agonists such as clonidine have been shown to decrease narcotic and volatile anesthetic requirements during surgery, to reduce plasma catecholamine levels, to improve hemodynamic stability, and to have potent analgesic properties (3–8). Unfortunately, clonidine is known to have a ceiling effect that limits its anesthetic actions (5). This limited potency may be due to clonidine's α_1-agonist properties, which manifest themselves at higher doses. The ceiling phenomenon observed with clonidine has led to a search for more potent and specific agonists of the α_2-receptor.

Dexmedetomidine is an α-adrenergic agonist that is 10–100 times more selective for the α_2-receptor than is clonidine (9). Dexmedetomidine has been shown to produce more than a 90% reduction in anesthetic requirements in dogs and rats (10,11). In studies involving human volunteers, dexmedetomidine (approximately 1 μg/kg) reduced blood pressure, heart rate, and plasma noradrenaline levels while producing pronounced sedation (12). Because of the potential for use of this drug as a clinical anesthetic agent, we investigated the effects of dexmedetomidine on the electroencephalogram (EEG), cerebral blood flow (CBF), and cerebral metabolic rate for oxygen ($CMRO_2$) in isoflurane-anesthetized dogs after the administration of 10 μg/kg, a dose that has previously

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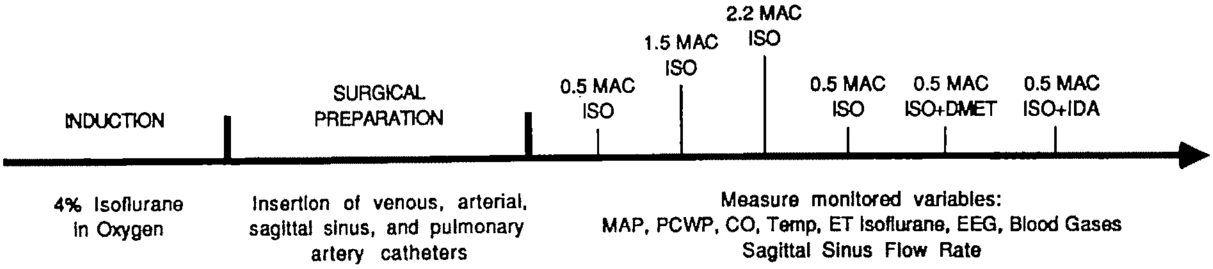
INDUCTION
SURGICAL PREPARATION
0.5 MAC ISO
1.5 MAC ISO
2.2 MAC ISO
0.5 MAC ISO
0.5 MAC ISO+DMET
0.5 MAC ISO+IDA
4% Isoflurane in Oxygen
Insertion of venous, arterial, sagittal sinus, and pulmonary artery catheters
Measure monitored variables:
MAP, PCWP, CO, Temp, ET Isoflurane, EEG, Blood Gases
Sagittal Sinus Flow Rate

Figure 1. Summary of experimental protocol. MAC, minimum alveolar concentration; ISO, isoflurane; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; ET, end-tidal; DMET, dexmedetomidine; IDA, idazoxan.

been shown to reduce anesthetic requirements by >90% (10). The α_2-adrenergic antagonist idazoxan was subsequently administered in an attempt to reverse the effects produced by the dexmedetomidine and thereby demonstrate their mediation via the α_2-receptor.

Methods

After approval from the Animal Use Committee, six mongrel dogs weighing 22 ± 1.6 kg (mean ± SEM) were initially anesthetized with 4% isoflurane in oxygen by mask. After loss of consciousness, an intravenous catheter was inserted in a foreleg vein and 3 mg of pancuronium was administered to facilitate endotracheal intubation. This was followed by a continuous infusion of pancuronium at a rate of 0.16 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$. The lungs were mechanically ventilated with 1.5%–2.0% isoflurane in oxygen to produce an end-tidal CO_2 of 35–40 mm Hg. Body temperature was servo-controlled to an esophageal temperature of 37°C. Femoral arterial and venous catheters were inserted via a groin incision, and a thermodilution catheter was positioned in the pulmonary artery via the right external jugular vein for measurement of cardiac output (CO), pulmonary arterial pressure, and pulmonary capillary wedge pressure. Cerebral blood flow was measured using a venous outflow technique previously described (13). Briefly, the scalp was incised in the midline and reflected laterally to expose the skull. To isolate cerebral venous drainage from extracranial sources, bilateral portions of the frontoparietal bone were removed with a high-speed drill, and the diploic veins were occluded with bone wax. The paired ethmoidal veins were exposed and occluded with bipolar cautery. The animals were heparinized (300 U/kg followed by 100 $U{\cdot}kg^{-1}{\cdot}h^{-1}$), and a sagittal sinus catheter was placed for the measurement of CBF (timed collections) and sampling of sagittal sinus blood. Bilateral fronto-occipital electrodes were cemented to the skull for recording of the EEG.

After completion of the surgical preparation, all wounds were infiltrated with 0.25% bupivacaine and the inspired isoflurane concentration was decreased to produce an end-tidal concentration equivalent to 0.5 MAC. (MAC, or minimum alveolar concentration, is a commonly used measure of anesthetic potency. It is defined as that concentration of volatile anesthetic that will prevent purposeful movement in response to an incision in 50% of the subjects. One MAC isoflurane in the dog equals an end-tidal concentration of 1.28% [14].) The animals were left undisturbed for a period of 15 min during which time auditory and tactile stimulation were avoided. Control values were then recorded for the monitored variables, which included mean arterial pressure, pulmonary artery systolic and diastolic pressures, pulmonary capillary wedge pressure, CO, temperature, end-tidal isoflurane concentration (Puritan-Bennett Anesthetic Agent Monitor, Wilmington, Mass.), EEG, sagittal sinus and arterial blood gas tensions. Sagittal sinus blood flow rates were measured in triplicate over a 10-min period.

The end-tidal isoflurane concentration was then increased to 1.5 MAC (1.9%), to 2.2 MAC (appearance of a burst-suppressed pattern on the EEG), and then back to 0.5 MAC. After each end-tidal concentration of isoflurane was achieved, a period of 15 min elapsed before recording the values of each of the monitored variables. Isoflurane was continued at a 0.5 MAC concentration, and dexmedetomidine (10 μg/kg; Farmos Group Ltd., Turku, Finland) was given by an infusion pump over a 10-min period. An additional 15 min elapsed before the monitored variables were again recorded. Finally, 0.3 mg/kg of the α_2-antagonist idazoxan (Reckitt & Coleman, Kingston-upon-Hull, U.K.) was infused over a 5-min period (Figure 1). This concentration of idazoxan has been shown previously to antagonize fully the anesthetic and hemodynamic properties of the α_2-agonist azepexole in dogs (15). Monitored variables were again recorded, after which the dogs were killed and their brains removed for measurement of wet weight.

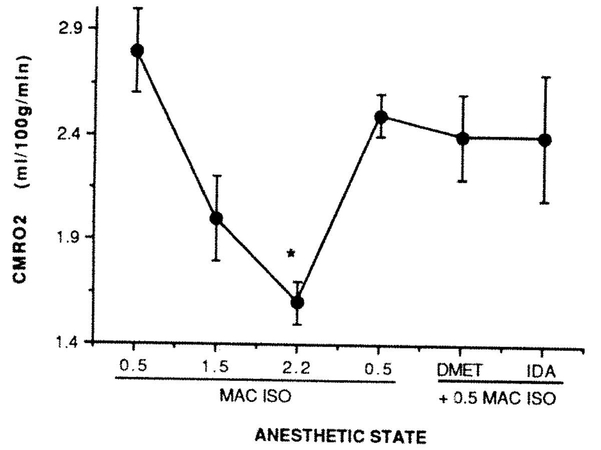

Figure 2. Mean (±SEM) global $CMRo_2$ at each anesthetic state during experiment. $CMRo_2$ was significantly decreased at 2.2 MAC isoflurane when compared with the dexmedetomidine + 0.5 MAC isoflurane state ($P < 0.01$). Abbreviations as in Figure 1. *$P < 0.01$, $n = 6$.

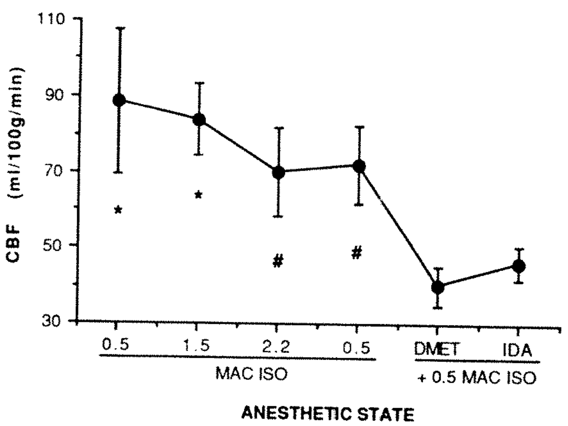

Figure 3. Mean (±SEM) CBF at each anesthetic state during the experiment. Cerebral blood flow decreased significantly after the administration of dexmedetomidine as compared with 0.5, 1.5, and 2.2 MAC isoflurane states. Abbreviations as in Figure 1. *$P < 0.01$, #$0.01 \leq P < 0.05$, $n = 6$.

Global CBF in milliliters per 100 g per minute was calculated from the mean sagittal sinus flow rate for each anesthetic state, as has been previously described (16). Blood oxygen contents adjusted for pH were calculated for arterial and sagittal sinus blood based on measurements of oxyhemoglobin concentration (IL 282 co-oximeter) and Po_2 (IL 813). Cerebral metabolic rate for oxygen was calculated as the product of the arterial-sagittal sinus oxygen content differences and the corresponding CBF.

Means are reported as ±SEM. Data were analyzed using a repeated measures analysis of variance followed by Dunnett's test where indicated to compare data obtained with 0.5 MAC isoflurane + dexmedetomidine to values obtained with the other anesthetic states.

Results

All blood flow/metabolic rate measurements for a given animal were completed within a 3-h period. Esophageal temperature ranged between 36.5° and 37.0°C. Mean arterial Pco_2 values were maintained between 36 and 38 mm Hg.

As expected, increasing concentrations of isoflurane resulted in decreases in the $CMRo_2$ (Figure 2). At 2.2 MAC isoflurane (EEG pattern of burst-suppression), $CMRo_2$ had decreased to 58% of the initial 0.5 MAC isoflurane value and was significantly less than that observed after the administration of dexmedetomidine ($P < 0.01$). Dexmedetomidine resulted in a $CMRo_2$ that was intermediate in magnitude and statistically no different from values obtained with 0.5 and 1.5 MAC isoflurane. There were no other statistically significant differences in $CMRo_2$ as compared with the 0.5 MAC isoflurane + dexmedetomidine state.

The administration of 10 μg/kg of dexmedetomidine resulted in a profound reduction in CBF when compared with the 0.5, 1.5, and 2.2 MAC isoflurane states ($P < 0.05$) (Figure 3). Cerebral blood flow fell from 72 ± 10 $mL \cdot 100\ g^{-1} \cdot min^{-1}$ at the second 0.5 MAC isoflurane determination to 40 ± 5 $mL \cdot 100\ g^{-1} \cdot min^{-1}$ after administration of dexmedetomidine (45% reduction). A reduction in CBF after the administration of dexmedetomidine was seen in all animals despite a concomitant increase in arterial pressure. The administration of 0.3 mg/kg of idazoxan resulted in an insignificant increase in CBF to a value that was not different from the 0.5 MAC isoflurane + dexmedetomidine state.

Mean arterial pressure increased significantly after the administration of dexmedetomidine (to 183 ± 16 mm Hg) as compared with the values obtained at 1.5 MAC, 2.2 MAC, or either of the 0.5 MAC states (138 ± 15 and 140 ± 16 mm Hg) (Figure 4). The administration of dexmedetomidine also resulted in marked increases in pulmonary capillary wedge pressure and pulmonary artery diastolic pressure (Table 1). These changes were associated with a significant decrease in CO (to 0.9 L/min, a 57% reduction from the values obtained at the second 0.5 MAC isoflurane state) (Figure 5) and heart rate.

Inspection of the EEG tracings revealed a progression from a predominance of high-frequency, low-amplitude waves at 0.5 MAC isoflurane to a burst-suppressed pattern at 2.2 MAC isoflurane. Administration of dexmedetomidine in the presence of 0.5 MAC isoflurane resulted in the loss of some of the high-frequency component and the appearance of

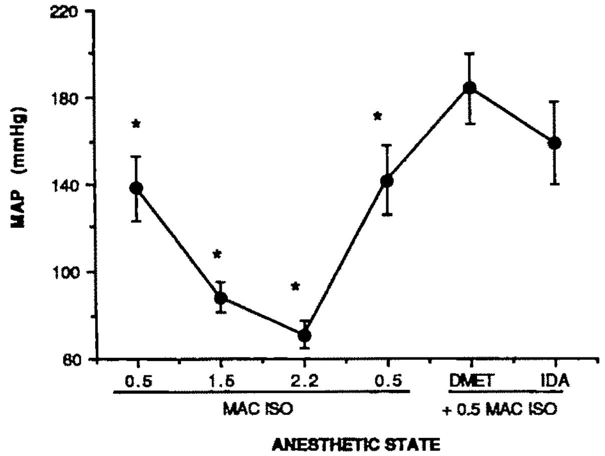

Figure 4. Mean (±SEM) arterial pressure at the various anesthetic states. Mean arterial pressure was significantly increased after the dexmedetomidine as compared with the 0.5, 1.5, and 2.2 MAC isoflurane states. Abbreviations as in Figure 1. *$P < 0.01$, $n = 6$.

high-amplitude slow waves similar to those seen at 1.5 MAC isoflurane. These changes were reversed after the administration of idazoxan (Figure 6).

Discussion

Dexmedetomidine is a potent and selective agonist of the α_2-adrenergic receptor. It has been shown to be capable of producing a reduction of >90% in volatile anesthetic requirement in dogs and rats (10,11). The anesthetic properties of this drug have been ascribed to activation of postsynaptic α_2-receptors and/or decreased noradrenergic neurotransmission in the central nervous system via dexmedetomidine's activation of the presynaptic α_2-receptor. Because of interest in the clinical use of this drug as an anesthetic agent, this study sought to determine the cerebral effects (CBF and $CMRo_2$) of dexmedetomidine. The study was designed to allow comparisons between dexmedetomidine-treated animals with anesthetic states that were "lighter" (e.g., 0.5 MAC isoflurane), "deeper" (e.g., 2.2 MAC isoflurane), and approximately equal (e.g., 1.5 MAC isoflurane).

The animal preparation employed in this study has been validated and extensively used to examine the effects of various other agents on CBF and cerebral metabolism (16,17). In the present study, the observed decreases in cerebral metabolic rate with increasing concentrations of isoflurane are consistent with previous reports (17,18). Cerebral blood flow values were observed to decrease between the initial 0.5 MAC isoflurane value (88 $mL \cdot 100\ g^{-1} \cdot min^{-1}$) and the second 0.5 MAC isoflurane state (72 $mL \cdot 100\ g^{-1} \cdot min^{-1}$). This corresponds to an approximately 10% per hour decrease in flow and has been previously described (16). Even if allowance is made for this time-dependent flow decrement, the effect of dexmedetomidine on CBF remains highly significant ($P < 0.05$ vs 0.5, 1.5, and 2.2 MAC isoflurane). The fact that significance could be demonstrated with only six animals is testimony to the magnitude of this effect.

Although it would have been desirable to study the effects of various dosages of dexmedetomidine, the time constraints imposed by the protocol allowed only a single dose to be examined. Ten micrograms per kilogram was selected for study as this amount produces a clinically relevant state in the dog (e.g., approximately 1 MAC of anesthesia). Even though a formal examination of other dosages could not be accomplished in these six animals, there was no evidence of a biphasic response in any of the continuously monitored variables during the course of the 10-min infusion of dexmedetomidine.

In this study, the administration of dexmedetomidine resulted in a significant decrease in CBF when compared with any of the preceding levels of isoflurane anesthesia. This decrease in flow occurred despite an associated increase in mean arterial pressure and no change in $CMRo_2$. Despite the striking decrease in the CBF/$CMRo_2$ ratio, the mean sagittal sinus Po_2 after dexmedetomidine administration was 46 mm Hg (Table 1). This suggests that there was no significant global ischemia and that the EEG alterations observed were due to the anesthetic actions of dexmedetomidine as opposed to inadequate oxygen delivery. It is important to note that these experiments were conducted in neurologically normal animals. The effect of a global flow reduction of this magnitude on brain regions with initially marginal perfusion cannot be predicted.

Other α_2-agonists (e.g., clonidine) have been reported to cause reductions in CBF of 36% in cats and up to 28% in humans (19,20). These flow changes appear to be mediated by increases in cerebral vascular resistance due to the stimulation of postsynaptic α_2-adrenergic receptors located on the cerebral vessels (21). The dexmedetomidine-associated decrease in CBF seen in the present experiment may have been due to such an α_2-receptor-mediated vasoconstriction of cerebral resistance vessels. It has been established that stimulation of the sympathetic nervous system by hypovolemic hypotension may result in cerebral vasoconstriction via activation of α_2-adrenergic receptors and that this vasoconstriction can be prevented by the administration of the α_2-adrenergic antagonist yohimbine (22). Direct stimulation of the locus ceruleus with resultant activation of ascending norad-

Table 1. Anesthetic State

	0.5 MAC ISO	1.5 MAC ISO	2.2 MAC ISO	0.5 MAC ISO	0.5 MAC ISO + DMET	0.5 MAC ISO + IDA
ET isoflurane (%)	0.64 ± 0.02	1.90 ± 0.03^a	2.81 ± 0.09^a	0.67 ± 0.01	0.62 ± 0.02	0.63 ± 0.02
Heart rate (beats/min)	114 ± 6^a	117 ± 7^a	110 ± 7^b	110 ± 7^b	91 ± 7	94 ± 9
Temperature (°C)	37.0 ± 2.4	36.9 ± 2.2	36.5 ± 1.5	36.6 ± 3.6	36.7 ± 3.8	36.9 ± 3.5
PA pressures (mm Hg)						
PA systolic	19.3 ± 2.5	18.1 ± 1.1	21.1 ± 1.9	21.3 ± 1.6	24.8 ± 3.0	23.3 ± 3.2
PA diastolic	8.1 ± 1.2^a	9 ± 0.7^a	10.5 ± 1.6^b	9.5 ± 0.8^b	16.3 ± 2.7	11.6 ± 1.4^b
PCWP	4.6 ± 1.1^a	5.1 ± 0.7^a	8.5 ± 1.3^a	5.5 ± 0.5^a	15.3 ± 3.5	8.3 ± 1.3^a
Arterial blood						
pH	7.32 ± 0.01	7.32 ± 0.02	7.34 ± 0.02	7.33 ± 0.02	7.31 ± 0.01	7.32 ± 0.02
$Paco_2$ (mm Hg)	38 ± 1	38 ± 1	36 ± 1	36 ± 0	38 ± 0	38 ± 1
Pao_2 (mm Hg)	518 ± 27	516 ± 20	505 ± 16	533 ± 24	531 ± 18	529 ± 16
BE (mEq/L)	−5.9 ± 0.4	−5.4 ± 0.7	−5.4 ± 0.7	−5.6 ± 1.0	−6.6 ± 0.9	−5.5 ± 1.0
Sagittal sinus blood						
pH	7.26 ± 0.01	7.29 ± 0.01^a	7.27 ± 0.02^b	7.26 ± 0.02	7.24 ± 0.02	7.23 ± 0.02
$Paco_2$ (mm Hg)	51 ± 1^a	48 ± 1^a	49 ± 2^a	53 ± 1^a	58 ± 2	58 ± 2
Pao_2 (mm Hg)	70 ± 10^a	77 ± 6^a	80 ± 12^a	60 ± 6	46 ± 6	50 ± 3
BE (mEq/L)	−4.5 ± 0.3	−4.1 ± 0.8	−4.4 ± 1.0	−3.9 ± 1.1	−3.8 ± 0.6	−4.2 ± 1.2

BE, base excess; DMET, dexmedetomidine; ET, end-tidal; IDA, idazoxan; ISO, isoflurane; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure.

All values are mean ± SEM. n = 6.

[a] $P < 0.01$, [b] $0.01 < P < 0.05$ vs 0.5 MAC ISO + DMET by analysis of variance followed by Dunnett's test.

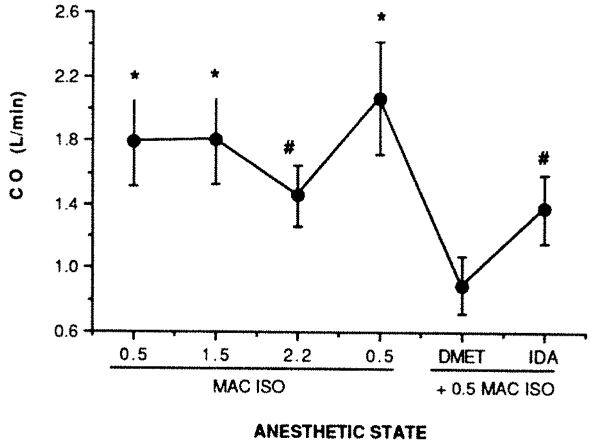

Figure 5. Mean (±SEM) values for CO during the experiment. Cardiac output was significantly decreased after the infusion of dexmedetomidine when compared with all other anesthetic states. Abbreviations as in Figure 1. *$P < 0.01$, #$0.01 \le P < 0.05$, $n = 6$.

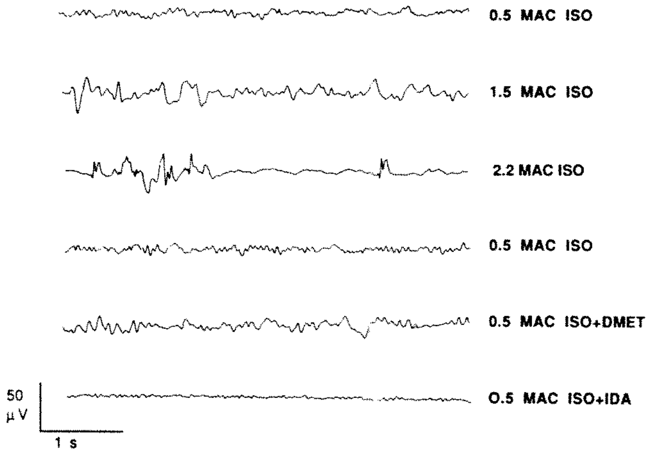

Figure 6. Typical alterations observed in the EEG. High-frequency, low-amplitude activity predominates with 0.5 MAC isoflurane. Slow wave activity becomes evident at 1.5 MAC isoflurane and this progresses to a burst-suppressed pattern at 2.2 MAC isoflurane. The administration of dexmedetomidine in the presence of 0.5 MAC isoflurane results in a pattern similar to that seen with 1.5 MAC isoflurane. Idazoxan caused the EEG pattern to revert to a high-frequency, low-amplitude pattern.

renergic fibers has also been shown to result in decreased regional CBF in those areas innervated by this system (23,24). An alternative explanation for the decrease in CBF observed in these experiments is that it was secondary to the decrease in CO. This explanation is less likely as CBF is generally believed to remain constant even in the face of drastic reductions in CO if mean arterial pressure is maintained above a lower limit of approximately 50 mm Hg. In these experiments, mean arterial pressure *increased* after the administration of dexmedetomidine and was far above the lower limit of autoregulation.

There was a statistically insignificant decrease in global $CMRo_2$ after the administration of dexmedetomidine to a value intermediate between those obtained with 0.5 and 1.5 MAC isoflurane. It may well be that the anesthetic state produced by dexmedetomidine is not due to a generalized depression of cortical function as is thought to occur with isoflurane and barbiturates, but rather to an inhibition of specific brain regions that contain dense concentrations of α_2-receptors. Production of an anesthetic state without a decrease in $CMRo_2$ would not be unique, as it is known to occur after the administration of the intravenous anesthetic ketamine (25).

The locus ceruleus may partially mediate dexmedetomidine's anesthetic effects through its extensive ascending and descending noradrenergic projections (26). Previous studies have shown that bilateral destruction of the locus ceruleus or interruption of its projections reduces anesthetic requirements in the rat (27). Furthermore, it has been demonstrated that either the systemic or microiontophoretic application of clonidine results in decreased firing of noradrenergic neurons in the locus ceruleus (28). If dexmedetomidine exerts its anesthetic actions via specific pathways, techniques capable of measuring regional rather than global cerebral metabolic rate may be necessary to detect drug-induced alterations.

Idazoxan (0.3 mg/kg) was successful in reversing the CO and EEG effects of dexmedetomidine. Idazoxan resulted in an insignificant increase in CBF and decrease in blood pressure. The failure to reverse these effects may have been due to an inadequate dose of the idazoxan. Although 0.3 mg/kg idazoxan prevented the bradycardia and MAC reduction achieved in previous experiments using the α_2-agonist azepexole, it appears that dexmedetomidine is a more potent agonist at the α_2-receptor and that this may necessitate an increase in the dose of the antagonist.

In summary, the administration of the α_2-agonist dexmedetomidine to isoflurane-anesthetized dogs resulted in a marked reduction in CBF with little or no change in $CMRo_2$. The observed reduction in CBF was probably due to an increase in cerebral vascular resistance mediated through postsynaptic α_2-receptors. Despite the large reduction in the CBF/$CMRo_2$ ratio, there was no global evidence of cerebral ischemia. The inability to detect a change in global $CMRo_2$ may be a result of dexmedetomidine acting on specific brain regions with dense populations of α_2-receptors as opposed to producing a generalized depression of cerebral activity. These data represent the first measurements of the effects of dexmedetomidine on CBF and metabolic rate. These observations will provide the basis for further animal studies of the regional cerebral effects of α-adrenergic drugs and may aid in the analysis of data generated from ongoing human trials.

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Does Preoperative Antiplatelet Therapy Increase the Risk of Hemorrhagic Complications Associated With Regional Anesthesia?

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HORLOCKER TT, WEDEL DJ, OFFORD KP. Does preoperative antiplatelet therapy increase the risk of hemorrhagic complications associated with regional anesthesia? Anesth Analg 1990;70:631–4.

Hospital records of 805 patients given 1013 spinal or epidural anesthetics were retrospectively studied to determine whether preoperative antiplatelet medications were significantly related to the development of hemorrhagic complications. Preoperative antiplatelet medications were taken by 391 (39%) patients, including 113 patients receiving multiple drugs. No patient developed signs of spinal hematoma or postoperative neurologic deficits. However, patients receiving antiplatelet medications had an increased incidence of "minor" hemorrhagic complications such as blood-tinged cerebrospinal fluid or blood aspirated through the spinal or epidural needle or catheter ($P < 0.05$). When considered independently as risk factors, age and epidural anesthesia were not statistically significant determinants of the incidence of minor hemorrhagic complications. The combination of increased age and epidural (but not spinal) anesthesia was associated with a 4.5% incidence of minor hemorrhagic complications ($P < 0.05$). Aspiration of blood through the spinal or epidural needle may not imply an increased risk for serious hemorrhagic complications. Clinical and laboratory screening of patients for preexisting coagulopathies and atraumatic needle placement may reduce the risk of minor hemorrhagic complications involved in patients given antiplatelet medications before the induction of regional anesthesia.

Key Words: BLOOD, COAGULATION—anticoagulant risks. ANESTHETIC TECHNIQUES, SPINAL AND EPIDURAL.

Spinal anesthesia has been shown to be generally free of serious hemorrhagic complications as demonstrated by a combined series totalling more than 40,000 spinal anesthetics (1–3). No factors predisposing to hemorrhagic complications such as coagulopathy, thrombocytopenia, anticoagulation, and antiplatelet therapy were evaluated, however, in these studies. In addition, Phillips et al. (4) reported no serious hemorrhagic complications in 10,440 spinal anesthetics even in the presence of a 3% incidence of bloody taps and a 6% incidence of multiple attempts at needle placement, two conditions suggesting traumatic needle placement.

Antiplatelet therapy, including medications such as aspirin, naproxen, piroxicam, and dipyridamole, has been considered a relative contraindication to epidural or spinal anesthesia due to the associated prolongation of bleeding time and theoretically greater risk of hematoma formation (5). In a review of the literature over the past 75 yr, Owens et al. cited 34 cases of spinal hematoma presenting with neurologic dysfunction after attempted lumbar puncture, six of which involved the induction of spinal anesthesia (6). Antiplatelet therapy was implicated in two of the 34 (7,8).

It has been suggested that the Ivy bleeding time is the most reliable predictor of abnormal bleeding in patients receiving antiplatelet therapy scheduled for surgery or regional anesthetics (9). However, the "postaspirin" bleeding time is not always a reliable indicator of platelet function or hemostatic capability (10). Although the bleeding time may return to normal within 2–3 days after aspirin ingestion, platelet function may take up to 7 days to return to normal. It is, therefore, possible to have a normal bleeding time without normal platelet function. On the other hand, several studies have been unable to find any correlation between perioperative blood loss and aspirin-induced prolongation of bleeding time (11). Therefore, measurement of an Ivy bleeding time before induction of spinal or epidural anesthesia may not be helpful in identifying those patients at increased risk for spinal or epidural hematoma.

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Orthopedic patients undergoing major joint surgery often have chronic musculoskeletal pain or underlying inflammatory disease such as rheumatoid arthritis and are frequently medicated with antiplatelet drugs preoperatively. The administration of spinal or epidural anesthesia to a patient receiving antiplatelet therapy remains controversial and largely unstudied. Spinal hematomas, although relatively infrequent, are catastrophic events; only 44% of patients in Owens' series who developed neurologic complications postoperatively had partial or good neurologic recovery (6). The potential risk of hemorrhagic complications in patients on preoperative antiplatelet therapy needs further examination. This study was performed to determine whether preoperative antiplatelet medications were significantly related to the development of hemorrhagic complications.

Methods

Hospital records of 805 patients given 1013 epidural or spinal anesthetics who were undergoing orthopedic procedures were retrospectively studied following approval by our Institutional Review Board. Demographic data, including age, sex, date of surgery, and type of surgery (hip, knee, or other lower extremity), were recorded. Platelet count and any coagulation studies made were also recorded. Patients receiving preoperative antiplatelet medications and the total daily dosages were identified. As part of the Mayo Clinic registration process, patients are requested at the time of admission to list all prescription and nonprescription medications. Patients were also questioned on their preoperative drug therapy by their attending physician and nurse. The regional anesthetic technique used (spinal or epidural) was recorded, along with the amount of time an indwelling epidural catheter (if used) was left in place. Evidence of major hemorrhagic complications such as transient or permanent neurologic deficits or performance of an emergency decompression laminectomy, and minor hemorrhagic complications such as blood aspirated through the spinal or epidural needle, was sought by examining the anesthesia record and subsequent physician and nurse chart entries until hospital dismissal. It is surgical practice in our institution to comment each day on neurovascular integrity in postoperative orthopedic patients. The hospital records were examined for subsequent admissions resulting from possible neurologic sequelae.

Statistical analysis was performed using a conventional χ^2 test or two-tailed t-test, where applicable. Multivariable analysis utilizing logistic regression of numerous potential predictor variables with backward elimination of nonsignificant variables was also performed. $P < 0.05$ was considered statistically significant.

Results

Average age was 55 ± 20 yr (range 15–96 yr). There were 551 (54%) operations performed on males and 462 (46%) upon females. Surgical procedures included 348 hip, 492 knee, and 173 other lower extremity procedures, and were performed from 1981 to 1987 with 868 (86%) procedures occurring in 1985 and 1986.

There were 399 spinal anesthetics (39%) and 614 epidural anesthetics (61%). Epidural catheters were placed for 609 procedures and were removed postoperatively in all but 48 cases. Of these 48, 24 had an indwelling epidural catheter for 1 day, 18 for 2 days, and six for 3 days. Of the 399 spinal anesthetics, three were performed with an 18-gauge needle, 286 with a 22-gauge needle, three with a 23-gauge needle, 68 with a 25-gauge needle, and five with a 26-gauge needle. In 29 procedures, the needle gauge was unknown. Five spinals were performed after failure of an attempted epidural.

Platelet counts were made before 1005 of the 1013 procedures. In three cases significant thrombocytopenia was noted (platelet count <100,000); none were below 50,000. Sixteen of 188 preoperative prothrombin times were slightly increased, with values between 13 and 19 s; the remainder were within normal limits. All 74 activated partial thromboplastin times measured were in the normal range. Bleeding times were measured preoperatively only six times; all were in the normal range.

Preoperative antiplatelet medications were administered before 391 (39%) of the 1013 operations; in 113 multiple antiplatelet drugs were used. In 72 cases, the patient had been given two antiplatelet medications, and in 41 cases three or more preoperatively. Aspirin was the most frequently used antiplatelet drug. The total dose of aspirin (as listed in 149 cases) averaged 1889 mg. Other commonly reported antiplatelet medications included naproxen, piroxicam, and ibuprofen. Antiplatelet agents and their total daily dosages are listed in Table 1.

No patients developed signs of subarachnoid or epidural hematoma or postoperative neurologic deficits. Blood was aspirated through the epidural or spinal needle in 13 of 391 patients who had received antiplatelet medications preoperatively and in only 8

Table 1. Preoperative Antiplatelet Therapy and Minor Hemorrhagic Complications

Antiplatelet medication	n[a]	Dosage n[b]	Dosage mg	Minor hemorrhagic complications n[c]	%	P
Aspirin	209	149	1889	7	3.3	NS
Naproxen	57	44	739	2	3.5	NS
Piroxicam	50	41	20	1	2.0	NS
Ibuprofen	43	32	1438	0	0.0	NS
Indomethacin	32	25	93	1	3.1	NS
Dipyridomole	31	29	189	2	6.5	NS
Sulindac	19	15	377	0	0.0	NS

NS, not statistically significant.

[a] Total number of patients receiving antiplatelet medication(s) preoperatively.

[b] Number of patients in which total daily dose of preoperative antiplatelet medications was known.

[c] Number of patients receiving each antiplatelet medication who had minor hemorrhagic complications.

Table 2. Risk Factors for Minor Hemorrhagic Complications

Factor	Number of procedures	Minor hemorrhagic complications n	%
Gender			
Male	551	13	2.4
Female	462	8	1.7
Surgery			
Hip	348	10	2.9
Knee	492	6	1.2
Other	173	5	2.9
Anesthesia			
Epidural	614	16	2.6
Spinal	399	5	1.2
Antiplatelet medication			
Yes	391[a]	13	3.3
No	622	8	1.3

[a] $P < 0.05$ compared with no preoperative antiplatelet therapy.

of 622 patients not given antiplatelet therapy ($P < 0.05$) (Table 2).

The incidence of minor hemorrhagic complications was not statistically significantly related to age, gender, platelet count, activated partial thromboplastin time, prothrombin time, or bleeding time, although the last three tests were rarely performed in this population. No specific antiplatelet medication was a significant risk factor for minor hemorrhagic complications. Type of surgical procedure, multiple surgical procedures, spinal needle gauge, or presence of an indwelling epidural catheter did not significantly increase risk of minor hemorrhagic complications (Tables 2 and 3). Age and epidural anesthesia, when considered independently as risk factors, were not significantly related to the incidence of minor hemorrhagic complications, but, when combined, increased age and epidural (but not spinal) anesthesia were associated with a 4.5% incidence of minor hemorrhagic complications ($P < 0.05$) (Figure 1).

Discussion

The administration of spinal or epidural anesthesia to a patient receiving antiplatelet therapy remains controversial and largely unstudied. Serious hemorrhagic complications are relatively infrequent events; therefore, an occurrence of zero events does not necessarily mean the risk is zero. The absence of postoperative neurologic dysfunction in the 391 patients given spinal or epidural anesthesia who had been given preoperative antiplatelet therapy in this study places the maximum risk (with 99% confidence) as high as 1.32%.

Aspiration of blood through the spinal or epidural needle during the induction of anesthesia may not imply an increased risk for serious hemorrhagic complications. A prospective study is needed to clarify this issue. Also, blood aspirated through the spinal or epidural needle or catheter may not always be recorded on the anesthesia record, especially if the amount is small and its presence brief. Therefore, the actual number of minor hemorrhagic events may be higher than reported. It is interesting to note that in 80% of reported spinal hematomas occurring after lumbar puncture there was also concomitant thrombocytopenia, antiplatelet therapy, or coagulopathy, and in 62% the needle placement was described as difficult and/or traumatic (6). Our study would suggest that epidural technique and increased patient age may also be a factor when occurring concomitantly.

The theoretical advantages of regional over general anesthesia in the population of patients we studied include decreased incidences of cardiopulmonary complications, decreased need for transfusion, decreased incidence of deep venous thrombosis, as well as the benefits of postoperative analgesia (12,13). These advantages must be weighed against the potential risk of serious hemorrhagic complications in patients on preoperative antiplatelet therapy, a risk that is largely undefined and historically very minimal.

Our review suggests that patients receiving preoperative antiplatelet medications can safely undergo major regional anesthesia. Although the bleeding time is proposed to be the best predictor of hemostatic abnormality in patients given antiplatelet medications, a normal bleeding time does not guarantee normal platelet function. Likewise, an abnormal

Table 3. Age and Coagulation Tests in Patients With and Without Minor Hemorrhagic Complications

	Without minor hemorrhagic complications		With minor hemorrhagic complications		
	n	Mean ± SD	*n*	Mean ± SD	P^a
Age (yr)	992	55 ± 20	21	63 ± 16	NS
Platelet count (× 10^3)	984	304 ± 85	21	282 ± 90	NS
Prothrombin time (s)	182	11.7 ± 1.2	6	11.5 ± 0.5	NS
Activated partial thromboplastin time (s)	72	33.7 ± 26	2	31.4 ± 0.5	NS
Bleeding time (min)	6	4.1 ± 1.4	0	0	—

NS, not statistically significant; *n*, number of procedures in which patient's age or coagulation parameter(s) were known.
$^aP < 0.05$ was considered as significant.

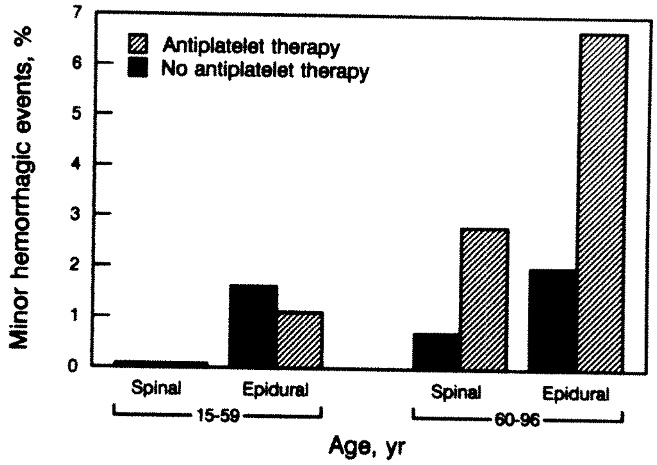

Figure 1. Risk profile for minor hemorrhagic complications utilizing multivariable analysis. Presence of antiplatelet therapy or age >60 yr accompanied by epidural technique increased the incidence of minor hemorrhagic complications ($P < 0.05$).

bleeding time is not consistently correlated with inadequate hemostasis and perioperative blood loss (7). Perhaps a more prudent approach to decreasing the risk of major hemorrhagic events associated with regional anesthesia would be to define which potential variables or combination of variables—such as coagulation parameters, a history of excessive bleeding or bruising, patient age, needle size, and anesthetic technique and expertise—are predictors of minor hemorrhagic events. The decision to perform a regional anesthetic in such patients could, therefore, be made on an individual basis, and the putative risk of a major hemorrhagic event could thus be minimized. Needle and catheter placement should be accomplished as atraumatically as possible, and the patient should be monitored closely in the perioperative period for early signs of cord compression. Immediate neurologic and radiologic evaluation should be performed at the first sign of pain in the back or legs, because neurologic recovery is poor if decompression is delayed (14).

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Ketamine Effects on Somatosensory Cortical Single Neurons and on Behavior in Rats

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PATEL IM, CHAPIN JK. Ketamine effects on somatosensory cortical single neurons and on behavior in rats. Anesth Analg 1990;70:635–44.

The neurophysiological effects of ketamine were studied at the single-neuron level in the somatosensory cortex of unanesthetized rats behaving in a treadmill movement paradigm. Chronically implanted 25-μm microwire electrodes were used to record spontaneous discharge, sensory responses, and sensorimotor-correlated activity of single neurons before and after ketamine administration. Extracellular action potentials of up to six single neurons were simultaneously recorded for several days, allowing ketamine effects to be tested repeatedly on the same neurons. Videotaped recordings obtained during each experiment were used to measure both the sensorimotor properties of the neurons and the changes in these measures caused by different doses of ketamine. Behaviorally, ketamine produced restless-hyperactive behavior at subanesthetic doses from 5 to 20 mg/kg (intramuscularly). At higher doses (30–50 mg/kg) the rats became cataleptic and immobile after the initial hyperactive period. Whereas the spontaneous rates of most neurons were reduced or unchanged after subanesthetic doses, a subgroup (27% of the total) exhibited markedly increased firing rates. This excitation was of a tonic nature, persisting for a dose-dependent duration in a manner that was not correlated with any of the behavioral effects of the drug. In further analyses, ketamine suppressed the sensory responses of virtually all of the recorded neurons. In particular, low doses of ketamine suppressed "sensorimotor" firing (mainly proprioceptive responses) of neurons in relation to active limb movement. It also suppressed virtually all neuronal sensory responses to the sudden onset of treadmill movement, although the time-course of this effect varied from neuron to neuron. These results reveal two separable effects of ketamine: (a) a strong inhibition of all somatosensory responsiveness in this area and (b) a tonic excitatory influence expressed heterogeneously on a subgroup of neurons. This coexistence of cortical neuronal excitation and sensory suppression in the same cortical region may explain in part the mechanism of dissociative anesthesia and hallucinatory side effects observed in humans during emergence from ketamine anesthesia.

Key Words: ANESTHETICS, INTRAVENOUS—ketamine.

The dissociative anesthetics, including ketamine and phencyclidine (PCP), are thought to induce analgesia by "disconnecting" the patient from his or her somatosensory environment. Instead of inducing a generalized central nervous system depression, these compounds can produce profound analgesia in the midst of a quasi-waking state, in which the eyes are wide open and spontaneous movements occur. During emergence from ketamine anesthesia patients are delirious and report strong feelings of disembodiment and a loss of the ability to distinguish self from non-self (1–6).

The term "dissociative anesthesia" was proposed by Corssen, Domino, and Miyasaka (7–9), whose pioneering electroencephalogram (EEG) studies suggested that ketamine acts by selectively depressing the neocortical association areas (as indicated by synchronized neocortical EEG) while increasing limbic system activity (as indicated by synchronized theta EEG over the hippocampus). Other studies involving EEG and evoked potentials have tended to confirm these observations (10). Furthermore, these conclusions have to a large extent been corroborated in studies using the 2-deoxyglucose technique to map grossly variations in the total metabolic activity over different regions of brain (11,12).

Unfortunately, the EEG and 2-deoxyglucose techniques provide only a gross and indirect measure of

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neural activity in a region. To obtain direct evidence as to the effects of a drug on either the firing activity or the sensory responsiveness of neurons, one must record from single cells individually. Interestingly, the few studies that have investigated the effects of ketamine on cortical neurons have been contradictory. In particular, Kayama and Iwama (13), who combined EEG and single-unit recordings in the sensorimotor cortex of cats after ketamine administration, reported variations in the cortical neurophysiology depending on the dose and/or the time-course of effect of ketamine. At low doses, or immediately after ketamine administration, a desynchronized EEG was seen, indicating arousal. At higher doses, a hypersynchronized EEG was recorded, which normally indicates slow-wave sleep. However, single neurons recorded in the sensorimotor cortex during these periods reportedly increased their firing rates. At still higher doses the EEG exhibited poly-spike wave complexes, and single neurons fired in bursts followed by long pauses. These phenomena were considered to be indicative of spontaneous seizure activity. Therefore, these authors agreed with the earlier conclusion of Mori et al. (14) that the hypersynchronous EEG produced by ketamine indicates an increased rather than a decreased activity state.

In light of these apparent contradictions, the present study was undertaken to reexamine the effect of ketamine on single-neuron discharge in the primary somatosensory (SI) cortex. This was motivated in part by a recognition that analysis of the effects of a drug on information processing in neural circuits cannot be understood simply by measuring overall increases or decreases in spontaneous discharge rates. Instead, one must investigate changes in normal neuronal responses to appropriate behavioral conditions and to applied sensory inputs. In previous studies (15), we have extensively mapped the variety of properties of neurons in the SI cortex in awake rats (15). These neurons exhibit cutaneous or deep somatosensory properties, or complex combinations thereof, or "motor-behavioral" properties (16). Thus, when considering the effect of ketamine on these circuits, one must consider which of these properties might be affected. Also, because the expression of each of these properties may be related to behavioral state, it is important to assess the behaviors that occur concomitant to the drug effects on neuronal discharge.

To address such questions, we have developed techniques for recording ensembles of single neurons (up to six) through arrays of microwire electrodes (MWEs) chronically implanted in the brain of awake, freely moving animals. This technique has several advantages over traditional neurophysiological approaches that utilize single-neuron recording in anesthetized animals. First, the ketamine effects can be compared with the activities of the same neurons in the drug-free condition. Second, one can correlate the drug's effect on neuronal activity in relation to different behavioral conditions. Third, single units recorded with implanted MWEs are relatively stable over long time periods, allowing recordings of the same neuron to be carried out until complete recovery from the drug, or even over multiple drug doses administered over several days. Fourth, because several neurons are recorded simultaneously, more data can be obtained in a given experiment. Finally and most importantly, the multiple-neuron recordings provide internal controls against the behavioral and pharmacokinetic variability normally associated with such studies.

Methods

Experiments were performed using 15 Long Evans rats weighing 200–450 g. The animals were kept on a 12-h light/12-h dark cycle and had free access to water and food ad libitum. About a week before the experiments, surgery was performed to implant the MWEs in the SI cortex. Each MWE consisted of 25-μm-diameter stainless steel Teflon insulated wire (California Fine Wire Company, Grover City, Calif.) with an uninsulated tip surface at the cut end. During implantation, the tips of the MWEs were kept about 100–200 μm apart to make sure that each MWE recorded a different neuron.

For implantation surgery the rats were anesthetized with pentobarbital (40–50 mg/kg, intraperitoneally [IP]) and mounted in the stereotaxic instrument. The skull was exposed and aligned so that bregma and lambda were on the same plane. A small (1 mm diameter) burr hole was drilled above the left primary SI cortex. Three ground screws were fixed in the skull surrounding the recording area (one each in the frontal, parietal, and occipital bones). Using a stereotaxic microdrive, the bundle of six recording MWEs with one ground wire was gradually lowered such that each MWE punctured the dura layer individually. Then the MWEs were lowered further to a depth of 0.8–1.2 mm in the cortex. The ground wire was connected with the ground screws on the skull. Finally, the whole assembly was fixed to the skull with dental acrylic cement.

During each experiment, the animal was placed within an enclosure (transparent plastic box, 40 × 20 × 40 cm) built over a treadmill that could be turned on–off by computer every 5 s to make the animal walk and rest in a cyclic fashion. This paradigm allowed us to identify neuronal firing properties in relation to the peripheral cutaneous sensory input from the right forepaw or hindpaw skin (electrodes were implanted in left sensory cortex) or proprioception/sensorimotor-related cells. Cutaneous receptive field were identified by touching the skin or hair with a wooden probe while listening to single unit firing through an audio amplifier. Occasionally, the discharge characteristics of the recorded neuron could not be correlated with any behavioral manipulation.

Electrophysiological Recordings

Extracellular action potentials from each MWE were amplified and filtered (removing very high and low frequencies). Normally, two or more action potentials of different sizes from each MWE were displayed on a dual-channel oscilloscope. Each signal was channeled through a separate discriminator adjusted to record action potentials having constant maximum voltage amplitudes. From there, the action potentials were fed again into the oscilloscope and simultaneously listened to through an audio amplifier system, as well as recorded in separate digital input channels on a Data General Microeclipse computer. This procedure allowed us to record simultaneously up to six single neurons in the rat cortex while the animal was freely moving as well as during ketamine-induced hyperactive and excited behaviors. Rarely, a cell was lost during the experiment, and occasionally a new cell appeared in a recording channel as judged by the changed firing patterns in relation to movement or drug effects. Only cells with a signal-to-noise ratio of 3:1 or more were recorded.

During each experiment, the recording typically involved (a) an initial 10–30-min predrug control period, or after intramuscular (IM) saline injection (same volume as in ketamine injections); (b) after ketamine injection; and (c) after recovery from the effects of the drug. Ketamine hydrochloride (5% or 10% Ketalar, Parke-Davis) was administered at a subanesthetic dose range of 5–50 mg/kg, intramuscularly, during different experiments. Because the duration of the ketamine effects was short (about 3 h or less, depending on a single dose), the experiments were repeated on the same or next day with the same or a different dose of ketamine. This also served as an internal control to compare the drug effects on the same neurons at different times. On some neurons the effects of ethanol (1–2 g/kg, IP, 20% in saline) were also recorded before or after ketamine injection.

Videotaped recording of the animals' behavioral responses was carried out to allow subsequent video frame-by-frame analysis of the different behavioral states and their correlation with the neuronal discharge rates. For this a Thalner (Ann Arbor, Mich.) video-frame timer was used to stamp the experimental time (with 10-ms accuracy) on each exposure-frame of the video record. This information was also analyzed later in relation to the electrophysiological data and the state of analgesia, defined as a state in which withdrawal of limbs in response to pinch with a toothed forcep could not be elicited.

Data Analysis

The computer was used to analyze quantitatively the histograms as follows. (a) Spontaneous firing rate (spikes per second or hertz) was averaged for 5-min time intervals over the entire recording duration. (b) Perievent histograms were constructed over the treadmill on–off cycles, revealing average instantaneous firing rates during movement and during rest. Such histograms were calculated and plotted for different 5–10-min time intervals before and after drug administration. Whenever applicable, percentage scores were used rather than absolute measures to normalize data obtained from different cells that usually had marked variations in spontaneous rate. These measurement techniques allowed quantitative comparisons to be made between magnitudes of specific neuronal responses during different behavior and drug states.

Results

During this investigation 80 single neurons were recorded in the SI cortex of 15 rats. The effects of different doses of ketamine on these neurons was tested by first recording their discharge properties during an initial 5–10-min control period, then administering ketamine and recording continuously until the animal recovered from both the behavioral and neurophysiological effects of the drug. In some cases, subsequent doses of ketamine or other drugs were administered. These experiments allowed us to test the effects of short- or long-term chronicity, to compare different doses of ketamine, and to compare the effects of different drugs on the same neurons.

Dose-Response of Ketamine Effects on Behavior

The first aim was to define the effects of ketamine on overall discharge rates of SI cortical neurons, espe-

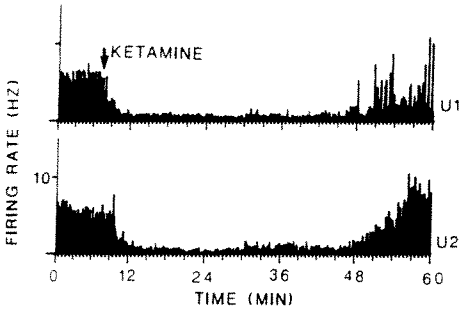

Figure 1. Inhibitory effect of ketamine on two simultaneously recorded SI cortical neurons. The two strip-chart histograms show the integrated activity of two single units (U1 and U2) recorded simultaneously over a 60-min experiment in a resting animal. Ketamine was injected after 10 min. Each histogram bin width represents 7.2-s recording time. Vertical axis ticks represent 10 spikes/s firing rate.

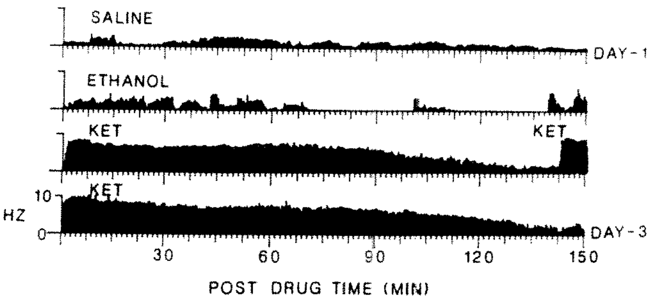

Figure 2. Excitatory effect of ketamine. Four strip-chart histograms show the integrated activity of a single SI cortical neuron over four 150-min recording periods. The recordings commenced just after injections of (from top): control saline, ethanol (1.5 g/kg), ketamine (KET; 50 mg/kg), followed by another ketamine injection at 140 min (KET). Two days later (DAY-3) ketamine was again administered, with similar effect. For both ethanol and ketamine, recovery from the drugs' effects were seen by 130–150 min postinjection. Scales are similar for all histograms. Each histogram bin covers 18-s recording time. Y-axis represents firing rate (10 Hz/tick).

cially in relation to different doses. For purposes of cross-species comparison it was first necessary to determine the effective doses of ketamine for induction of different levels of anesthesia, as determined through behavioral observation. A clear dose dependence was observed in the timing and degree of behavioral changes induced by ketamine. At very low doses (5–15 mg/kg), ketamine produced a distinctive behavioral response, characterized initially by restlessness, agitation, confusion, disorientation, and ataxia. Increased muscular and locomotor activities were also observed, manifested by alternate flexion-extension movements of the head, circling, rolling over, searching, and/or alternating right and left turning movements. A strong analgesia was also present at these doses, as indicated by the animals' failure to respond normally by leg withdrawal to pin-prick. At higher doses, the behavioral effects changed from this restlessness to a cataleptic state (from 20–50 mg/kg) and finally to anesthesia (above about 50 mg/kg). Increasing dose was also reflected in the total duration of the ketamine effect.

Effects of Ketamine on Neuronal Discharge Rates

Whereas subanesthetic doses of ketamine (5–50 mg/kg body wt, IM) produced both excitatory and inhibitory effects on SI cortical neurons, the inhibitory effect was most prevalent. About 60% of neurons in animals receiving subanesthetic doses exhibited reductions in discharge rate. Figure 1 illustrates the typical inhibitory effect of ketamine on two single neurons recorded simultaneously in the forepaw area of the SI cortex. After a 10-min control recording, ketamine (30 mg/kg, IM) was injected (at arrow). The period of strong suppression of the spontaneous discharge rates of these neurons was coupled with cataleptic, immobile behavior. After about 35 min postinjection the normal level of neuronal firing began to recover. The recovery to normal behavior followed a similar time-course.

Despite this predominance of inhibitory effects, a sizable minority of the recorded neurons (22 of 80) exhibited marked *increases* in spontaneous firing rates after administration of subanesthetic doses of ketamine. As an example, Figure 2 illustrates the activity of a single SI cortical neuron, which was recorded over a period of 3 days. On day 1 a control dose of normal saline (0.1 mL, IM) was administered, and the neuron was continuously recorded for 150 min. The animal rested for most of this time, although some periods of spontaneous movement occurred. This particular neuron tended to discharge at a higher rate during rest than during movement. Subsequently an injection of ethanol (1.5 g/kg, IP, 20% in normal saline) was made, and its effect on the neuron was recorded for another 150-min period. This depressant drug slightly increased the firing rate at first, but then reduced it. After 150 min the animal had fully recovered from the overt behavioral effects of the ethanol. At this time ketamine (50 mg/kg, IM) was injected. Within 2 min the neuron showed a marked increase in its firing rate; at the same time the animal began to exhibit behavioral hyperactivity, restlessness, and confusion. However, by 5 min after ketamine administration, the rat became cataleptic and immobile, a state that lasted for more than an hour. Thus, the firing rate increase appeared to be unrelated to the level of behavioral activity. This dissociation of neuronal activity from motor activity was again shown during recovery. As the neuronal firing gradually decreased over the subsequent 2 h, the rat remained cataleptic until behavioral hyperactivity was seen again during a sudden emergence from the drug effects. During this time the firing rate continued to decrease gradually, even though marked behavioral transitions were occurring. The increased movements did not alter the declining firing rate. When, 140 min after the first ketamine injection, another similar dose of ketamine was injected, similar neuronal excitation was produced. On day 3 ketamine was once again injected (50 mg/kg, IM). The development of neuronal excitation with initial behavioral hyperactivity for 4–5 min, followed by a cataleptic immobile state, was similar to that observed on day 1.

This dissociation of behavioral effect from firing rate was commonly observed among the neurons that were excited by ketamine. The degree of excitation of these neurons was dose-dependent up to the 10–15-mg/kg dose level, but, beyond this, further increases in firing rate were not generally observed by increasing the ketamine doses. However, further increases in dose did increase the duration of the ketamine-induced neuronal excitation and also of the cataleptic behavior.

Effects of Ketamine on Sensorimotor Properties

Further experiments were carried out to determine the extent to which the ketamine-induced changes in neuronal firing rate were related to effects on the sensorimotor properties of the SI cortical cells. To address this issue a standard experimental procedure was followed. First, the single recorded units were evaluated as to their general properties, including receptive fields, and also as to their pattern of discharge during movement. These units tended to exhibit either cutaneous, deep (mainly proprioceptive), or "complex" receptive fields, depending on the recording location within the SI cortex. Many of these neurons discharged predictably when their receptive fields were stimulated during the course of active movement. However, as we have previously reported (16), many other neurons fired robustly in correlation with active movement, even in the absence of any sensory receptive field that could explain this movement-related activity.

To quantify these spontaneous and movement-related firing patterns, a standardized movement behavior paradigm was employed using a motor-driven treadmill that was automatically switched on and off at 5-s intervals. This allowed us to record neuronal activity during repetitive periods of rest and movement. Characterization of ketamine's effects on the activity of these neurons in relation to specific phases of fore- or hindlimb movement was carried out through frame-by-frame analysis of synchronized videotaped records obtained during the experiments. In addition, the sudden onset of treadmill movement provided a time-locked stimulus capable of activating a variety of cutaneous and proprioceptive receptors. This stimulus provided a general test of neuronal responsiveness to significant natural sensory stimuli.

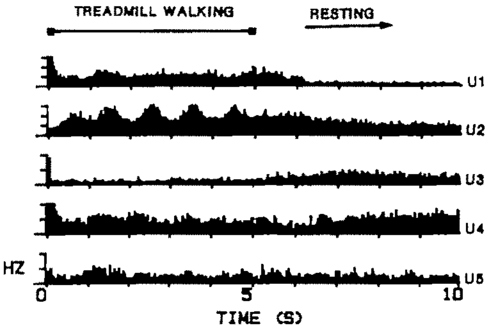

Figure 3. "Peritreadmill-ON" histograms of five simultaneously recorded single neurons (U1–U5) show differences in the discharge patterns of each neuron over 60 repetitions of a 5-s on/5-s off cycle of treadmill movement. In each histogram, the activity from 0 to 5 s represents the average firing of each neuron during treadmill walking. The activity from 5 to 10 s represents their discharge during resting. Bins = 20 ms. Y-axis tick mark = 10 spikes/s (Hz) firing rate.

As an example, Figure 3 contains "peritreadmill-onset histograms" showing the movement- and rest-related firing activity of five single neurons (U1–U5) simultaneously recorded in the SI cortical hindlimb area before administration of ketamine. Each histogram was constructed by averaging a neuron's activity over 60 repetitions of the treadmill cycle (5 s on/5 s off).

The histograms in Figure 3 illustrate several types of sensorimotor responses that are characteristic of neurons recorded in this area. The time-course of the rat's motor behavior over this cycle can be seen in the movement-correlated activity of the recorded neurons. For example, the treadmill was moving from 0 to 5 s in these histograms and was stopped from 5 to 10 s. It can be seen that unit 3 decreased its firing rate, whereas units 1 and 2 (U1, U2) increased their firing rates during the movement period. This firing during treadmill running was specifically correlated with the cycle of active locomotor movement of the hindlimb. After the treadmill stopped, the rat typically took one more step, which is reflected in the persistence of movement-related neuronal activity for about 1 s after the treadmill stopped.

To characterize further the activity of these neurons in relation to hindlimb movement, frame-by-frame analysis of videotaped records of this experiment was used to construct perievent histograms

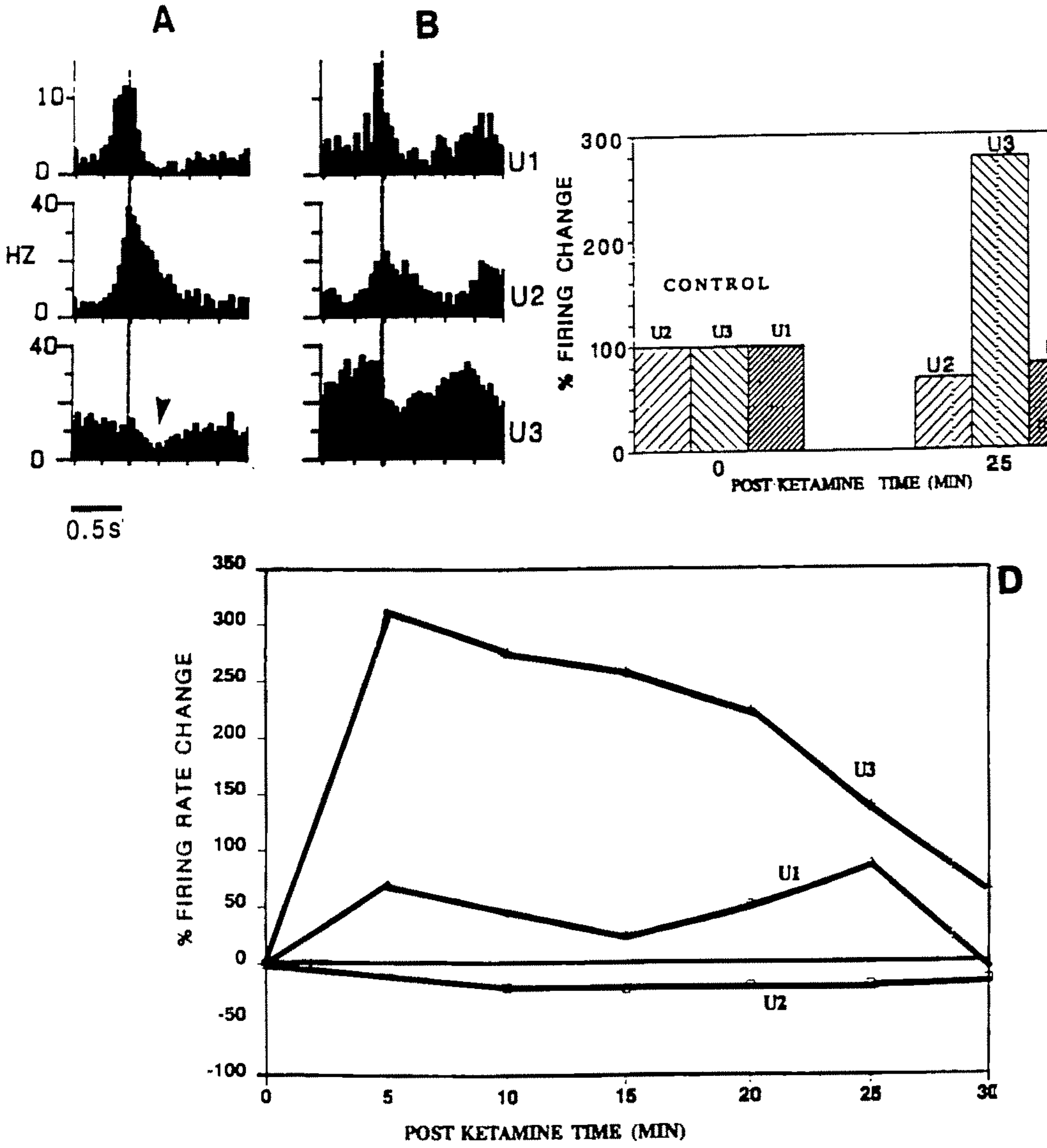

Figure 4. Ketamine effects on neuronal sensorimotor properties. Perievent histograms show averaged instantaneous firing rates of three neurons around 60 repetitions of onset of hindlimb flexion during treadmill locomotion. Flexion onset times determined by frame-by-frame analysis of videotaped records. *Dotted lines* represent onset of hindlimb flexion. A, Histograms of three simultaneously recorded single neurons (U1–U3). Whereas U1 and U2 fire in relation with the onset of flexion, U3 is inhibited soon after the responses of U1 and U2 (inhibition indicated by *arrow*). B, Similar perievent histograms made 25 min after ketamine injection (10 mg/kg, IM) show marked suppression of the firing activity of U1 and U2. The inhibitory response characteristic of U3 still persists but the firing rate of this neuron is markedly increased. Y-axis represents firing rate (spikes/s or Hz). C, Bar graph illustrates percentage change in firing rate of these three neurons during treadmill movement. Normalized control values are represented as 100% bars at 0 time. At 25 min postketamine, discharges of U1 and U2 were depressed, whereas U3 was excited. D, Line graph showing percentage changes in firing rates of these three neurons over all behaviors measured in 5-min intervals after ketamine.

triggered around the flexion movement that begins the swing phase of hindlimb stepping. Figure 4A contains histograms illustrating the step-cycle-related activity of neurons 1, 2, and 3 (U1, U2, and U3). It can be seen that unit 1 fired a burst of activity commencing during the flexion phase, whereas unit 2 commenced slightly earlier. The fact that units 1 and 2 fired strongly during certain phases of the hindlimb movement explains their overall increased activity during movement. Similarly, the fact that unit 3 showed a mainly inhibitory response during the swing phase explains its overall decreased activity during movement.

Because the ketamine-induced cortical neuronal excitation (as in Figure 2) was typically associated with increased locomotor activity at lower ketamine

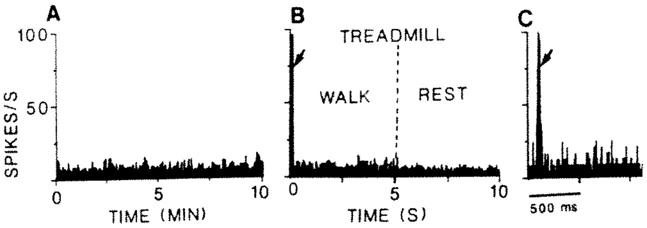

Figure 5. Sudden onset of treadmill movement provides a robust test for neuronal response to significant sensory stimuli. Here, a neuron was recorded during a 5-s on/5-s off treadmill movement cycle. **A**, Strip-chart record of the discharge of a single neuron over 10 min. Because each bin covers 1.2 s the neuron's responses to treadmill onset are averaged out. **B**, Peritreadmill-onset histogram shows the neuron's firing rate over the treadmill on/off cycle. Bins = 20 ms. Treadmill onset sensory response is visible (*arrow*). **C**, Similar histogram with 5-ms bins expanded around treadmill onset to show TOSR (*arrow*).

doses, the question arises as to whether this excitation was produced exclusively as a result of increased sensory input associated with the increased movements. Figure 4B shows equivalent histograms triggered around locomotor hindlimb flexion movements observed in videotaped records obtained after a 10-mg/kg dose of ketamine. Because the rat was cataleptic and not able to walk on the treadmill for 2–22 min after the ketamine injection, these perievent histograms were generated 25 min after ketamine injection, when the rat was again able to walk on the treadmill.

A comparison of the postketamine histograms in Figure 4B with their controls in Figure 4A shows that ketamine reduced the phasic-movement-correlated-discharge of unit 1 and, even more strongly, unit 2. These findings can be compared with the effects of ketamine on the firing rates of both of these units, which are graphed in Figures 4C and 4D. Figure 4D shows the percentage changes from control in overall firing rates of units 1, 2, and 3 calculated for each 5-min interval from 5 to 30 min after injection. In this, only unit 2, which suffered the strongest suppression of its sensorimotor response, exhibited an overall inhibition. By comparison, unit 1 was slightly increased, especially in the 5- and 25-min postinjection periods. These peaks in firing rate reflect the increased motor activity that occurred as the animal first entered and then emerged from a more catatonic level of anesthesia.

As a control for the effects of spontaneous movement, Figure 4C shows the percentage changes from control of the firing rates of these neurons during the treadmill-on periods 25–30 min after ketamine injection. This shows that, for the same approximate level of motor activity, both units 1 and 2 discharged at overall lower rates relative to control. Thus, for neurons such as these, whose firing rates were reduced by ketamine, a major cause of the reduction appeared to be a significant suppression of their normal sensorimotor responses.

On the other hand, the marked firing-rate increases characteristic of neurons such as unit 3 (Figures 4C and 4D) did not appear to be caused by ketamine-induced changes in sensorimotor responses. Figure 4B suggests that this strong increase was expressed over the whole step cycle, and was not caused by simply reducing the inhibitory sensorimotor response. In fact, this neuron showed its greatest firing-rate increase during the first 5-min period, when the animal exhibited the greatest hyperactivity.

It appears that ketamine has at least two separate effects on SI cortical neurons. The first is a suppression of specific sensorimotor properties, leading to an overall reduction of firing rate among most neurons, especially those possessing somatosensory receptive fields. The second effect is a more general excitation that is independent of sensorimotor properties. Indeed, the neurons that most strongly exhibit this excitatory effect tend to be those that are normally inhibited during movement. However, many of the neurons excited by ketamine did possess somatosensory receptive fields. In these, ketamine produced its excitatory effect despite the fact that their specific sensorimotor responses were strongly reduced.

Effects of Ketamine on Sensory Responses

An additional technique that was found to be useful in assessing the effects of ketamine on SI cortical neurons was to measure their sensory responses to the sudden onset of treadmill movement. We have found that most neurons with cutaneous receptive fields on the paws, or proprioceptive receptive fields in the limbs, respond robustly to the treadmill onset stimulus. This paradigm is also a useful test of cortical responsiveness to behaviorally significant environmental stimuli because treadmill onset is normally the cue to begin movement.

Such responses can be seen in Figure 3 in the histograms for units 1, 3, and 4, and, more clearly, in histograms B and C in Figure 5. Such responses are usually measured between 10 and 60 ms after treadmill onset. Analysis of videotaped records showed that the rat's first sign of movement began only after about 200 ms. Thus, this "treadmill onset sensory response" (TOSR) could be considered as purely sensory in nature because it occurs before any motor reaction. Thirty of the 80 (37%) single neurons recorded here exhibited such TOSRs. The magnitude of unit activity during this response varied from 25 to 60 spikes/s.

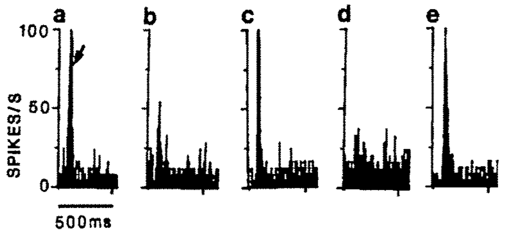

Figure 6. Effects of ketamine on the TOSR. The series of peritreadmill-onset histograms here show the TOSR of a single SI cortical neuron: (a) during a 10-min predrug control period; (b) 5 min after injection of ketamine (10 mg/kg, IM); (c) 3 h after the same ketamine dose; (d) 5 min after an additional ketamine dose (10 mg/kg) injected 3 h after the first; and (e) 3 h after the second ketamine injection. (All histograms are normalized to constant scale of instantaneous firing rate per bin [10 spike/s firing rate per bin].) Bin width = 5 ms. Horizontal scale ticks = 500 ms after treadmill was switched on by computer.

Figure 6 shows the effects of a 10-mg/kg dose of ketamine on such a TOSR (Figure 6a) of a single neuron recorded over two successive experiments. During the first experiment, ketamine (10 mg/kg, IM) was injected, rendering the animal ataxic and partially cataleptic. Five minutes after injection, the TOSR of the single neuron was strongly suppressed (Figure 6b). Recovery to the control level took 3 h (Figure 6c). One hour after ketamine injection, the animal's behavior was completely normal. Three hours later the experiment was repeated. Within 5 min after the administration of the same dose of ketamine, the TOSR was again suppressed (Figure 6d) simultaneously with the development of restlessness, ataxia, catalepsy, and disorientation. Again, almost complete recovery was observed 3 h after ketamine injection (Figure 6e). Ketamine did not markedly alter the latency (onset time) of the TOSR. However, the motor responses to the treadmill onset were severely delayed or absent.

Ketamine reduced or abolished virtually all of the TOSRs recorded in this study. As such, it is the most consistent of all the effects of ketamine we have observed. The universality of this sensory suppression raises the question of whether the effect might be exerted indirectly, e.g., at subcortical levels of the somatosensory pathway. If so, the TOSRs of SI cortical neurons might be expected to be relatively homogeneous in other respects, such as in the time-course of their suppression after ketamine. This possibility was addressed here by recording from multiple SI cortical neurons simultaneously through the whole time-course of a ketamine administration experiment. Figure 7 illustrates treadmill-onset histograms obtained from four neurons recorded simultaneously over a 5-h ketamine experiment. The sensory responses (Figure 7A) of each of these neurons were completely abolished 5 min after injection of ketamine (15 mg/kg, IM, Figure 7B). At this time, the animal was unable to walk on the treadmill because of the drug effect, and the treadmill was turned off for 25 min. When the animal was again able to maintain balance the treadmill on–off cycle was resumed. By 60 min nearly complete recovery of these sensory responses was observed in two neurons; no responses were present in the others (Figure 7C). After 200 min, partial recovery was observed in the two others (Figure 7D), but complete recovery was seen only after 300 min (Figure 7E). Thus, marked variability was observed in the time-course of the effects of ketamine on different cortical neurons, even though its overall effects were quite similar.

Discussion

This neurophysiological investigation revealed dose-dependent effects of ketamine on the spontaneous discharge activity and sensory responses of somatosensory cortical single neurons. At subanesthetic doses, about one-fourth of the recorded cortical neurons showed a marked excitation in the form of increased spontaneous firing rate, while at the same time others showed a strong suppression of sensory responsiveness and spontaneous discharge rates. Even at very low doses (5–15 mg/kg IM), ketamine markedly suppressed the sensorimotor properties of cortical sensory neurons, as reflected in their phasic activity related to limb movement. These low doses also strongly suppressed neuronal responses to the onset of treadmill movement.

These effects on the sensorimotor responses of single cortical neurons may be responsible, in part, for some of the effects of ketamine on movement, such as motor-incoordination, ataxia, and catalepsy. The suppression of responses to both cutaneous and proprioceptive inputs is also consistent with the dissociative effect of the drug. In particular, loss of proprioceptive sensation has long been linked to feelings of disembodiment (17), which are typical of ketamine and phencyclidine effects.

The pattern of sensory suppression caused by ketamine is to be distinguished from that caused by other anesthetics. For example, we have found that halothane and barbiturates (15) selectively suppress long-latency but not short-latency sensory responses, even at relatively deep anesthetic levels. Ketamine, on the other hand, powerfully suppressed all latencies of somatosensory responses, even in animals that continued to exhibit behavioral hyperactivity.

Also unlike other anesthetics, ketamine produced marked increases in firing rates of a sizable subset of

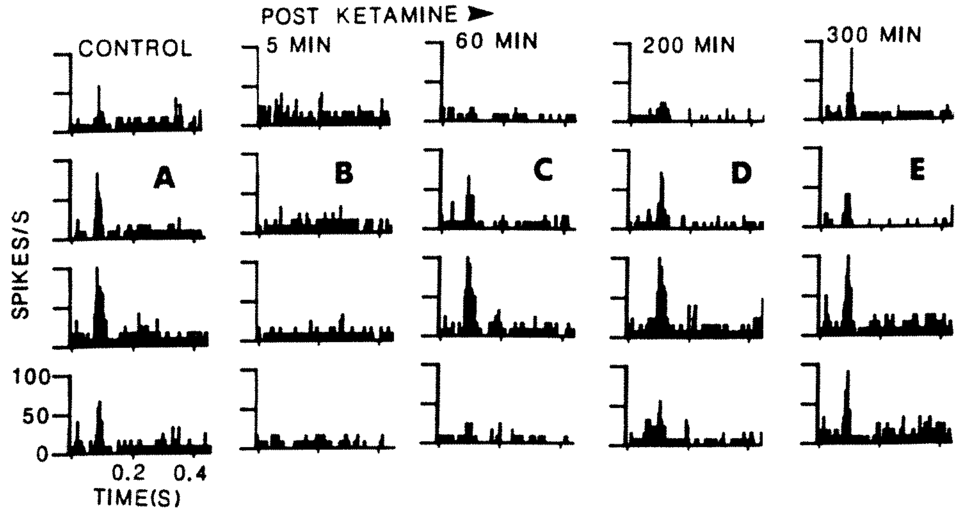

Figure 7. Four simultaneously recorded neurons show differential time-course of recovery from ketamine effect. Treadmill onset sensory responses of each neuron are shown in **A** during a 5-min control recording. **B**, All responses abolished 5 min after ketamine (15 mg/kg, IM). **C**, Sixty minutes after ketamine: two neurons completely recovered, two are still depressed. **D**, Two hundred minutes after ketamine: two neurons fully recovered, two have partial recovery. **E**, Complete recovery of all four neurons by 300 min. All histograms are normalized to constant scale of instantaneous firing rate (50 spikes/s per bin). Horizontal ticks = 0.2 s. Treadmill onset at 0.0 s.

SI cortical neurons. This is somewhat reminiscent of Kayama and Iwama's report (13) that ketamine produces cortical neuronal excitation. Our finding was different, however, in that only a relatively small subset of our neurons were excited, and also in that this excitation did not resemble seizure discharges.

This excitatory effect appeared to be independent of the normal sensory drive to the SI cortical neurons, because they typically lost their sensory responsiveness. This was paradoxical in that it appears that these neurons were disconnected from the circuits that normally drive them, yet showed markedly increased firing rates. The increased firing rates were also independent of motor activity, because they occurred during both the hyperactive and the cataleptic phases of ketamine's effects.

Results of the original EEG studies (7–9,18–20) suggested that the central effects of ketamine are mediated by depressing activity of somatosensory thalamocortical areas while activating limbic areas. Whereas our finding that somatosensory responses in the SI cortex are strongly suppressed by ketamine agrees with this theory, our discovery of strong excitatory influences on some neurons does not. Nevertheless, this combination of a universal somatosensory suppression with a behaviorally independent excitation of cortical neurons may contribute to the dissociative effect of this drug by replacing the normal sensory connection to the periphery with an unmodulated central excitatory drive.

Possible Mechanisms of Ketamine's Effect

Although it is difficult to speculate on the neurochemical basis of ketamine's effect on SI cortical neurons, the results of this study may provide some clues. One question, for example, is whether ketamine produces its effects directly or through metabolites, which would be expected to persist in the brain after removal of ketamine. This issue has been previously addressed by comparing the time-course of brain concentration of ketamine with its behavioral effects. It was shown that after intravenous administration of ketamine in rats there is a rapid increase in the brain concentration of ketamine (21,22), with maintenance of a high brain: plasma ratio as long as the behavioral effects persist. Here, the average time course of the neurophysiological effects of ketamine also matched the behavioral effects and did not suggest significant lingering effects. This indicates that ketamine itself, and not a metabolite, is the causal agent.

Another question is whether the observed effects of ketamine can be traced to specific actions on a specific endogenous neurotransmitter system. In particular, ketamine and other dissociative anesthetics are open channel blockers of the *N*-methyl-*d*-aspartate (NMDA) receptor and reduce NMDA-stimulated cation currents (23,24). In vivo, ketamine should strongly reduce the responses of already depolarized neurons to responses to endogenous excitatory amino acids. Cottman (24) has demonstrated high concentrations of NMDA receptors in all cortical structures of the rat. In the SI cortex these are especially dense in the superficial cortical layers, which are the primary regions for reception and initial processing of thalamocortical sensory inputs. An inhibition of excitatory synapses in these cortical layers is therefore consistent with our finding that ketamine strongly suppresses sensory responses in this region. By extension this would also explain the reduction in discharge rate of the neurons that normally receive such input.

However, this does not explain the source of the excitatory effects observed here among a subgroup of neurons. One could easily invoke a circuit explanation, e.g., ketamine may inhibit the cells that normally inhibit this subgroup. Alternatively, these or other effects of ketamine could be the result of actions on other neurotransmitter systems. For example, ketamine has been reported to have effects on the cholinergic system (25). One still has difficulty explaining the excitatory neurons, however, because these effects would still tend to inhibit neuronal firing. Furthermore, both of these effects required anesthetic doses of ketamine, whereas ketamine was able to reduce or block NMDA responses at subanesthetic doses. It appears, therefore, that no mechanism based purely on known interactions between ketamine and endogenous neurotransmitter systems can now be formulated to explain our results.

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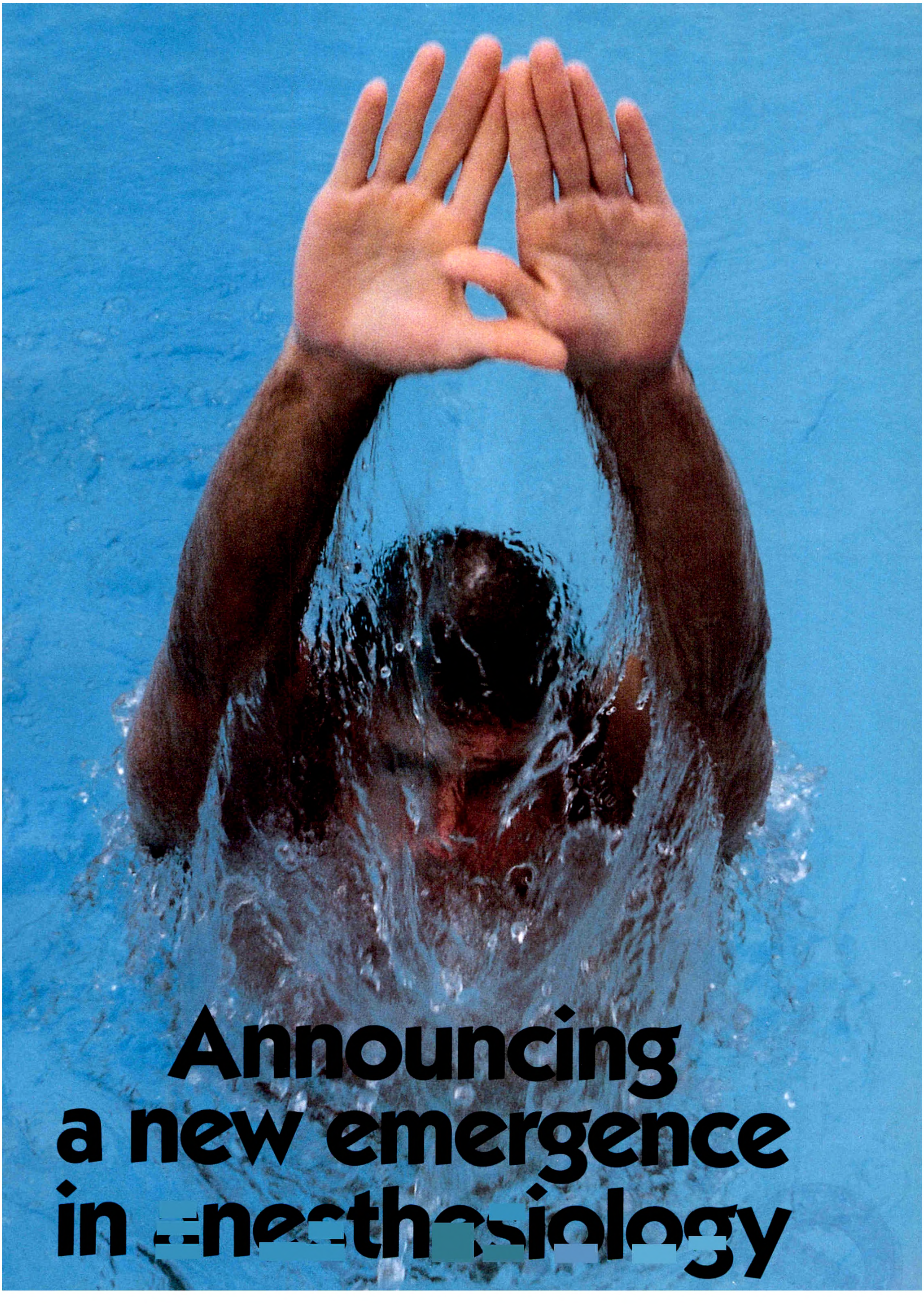
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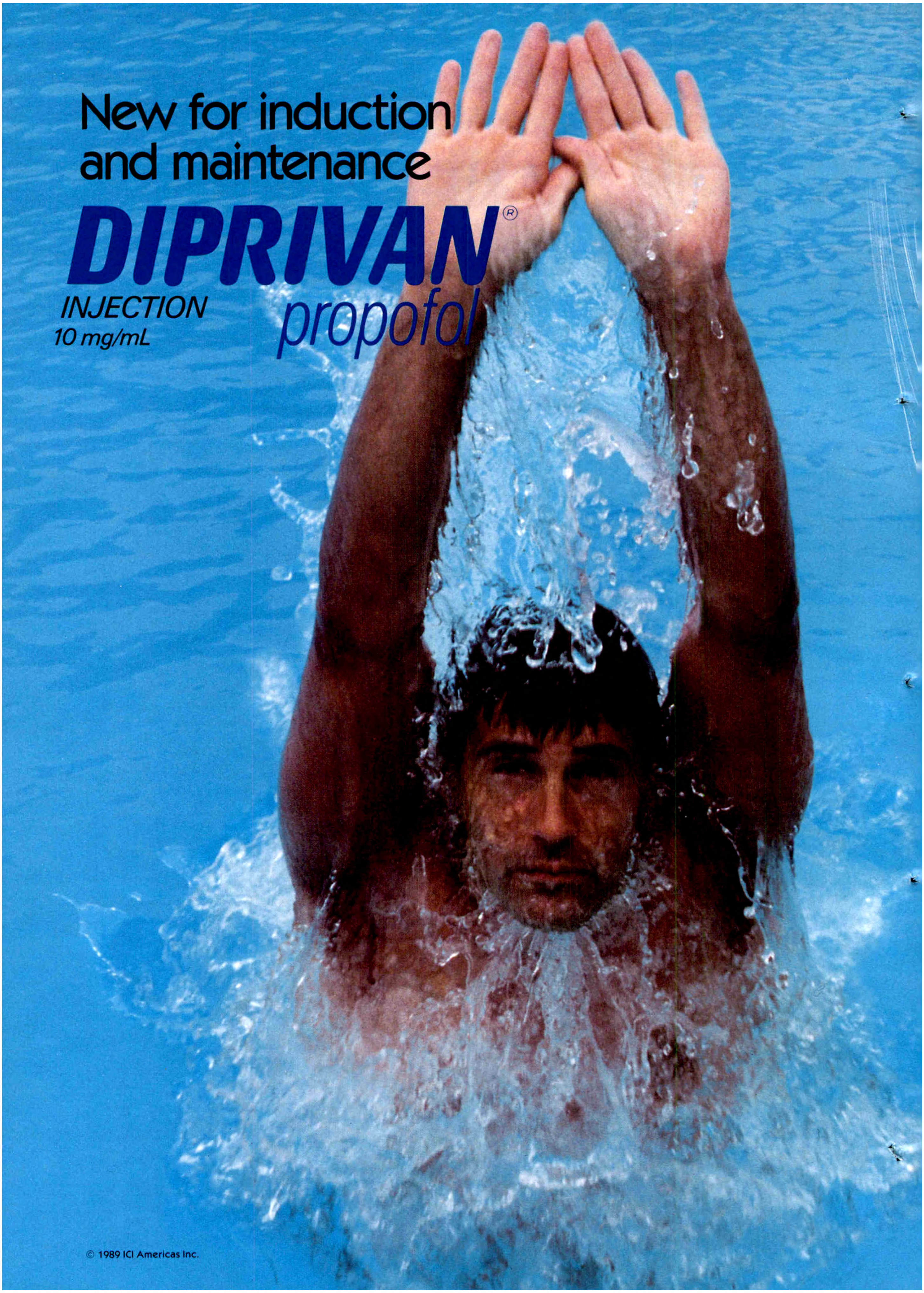
in anesthesiology



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Rapid, predictable onset

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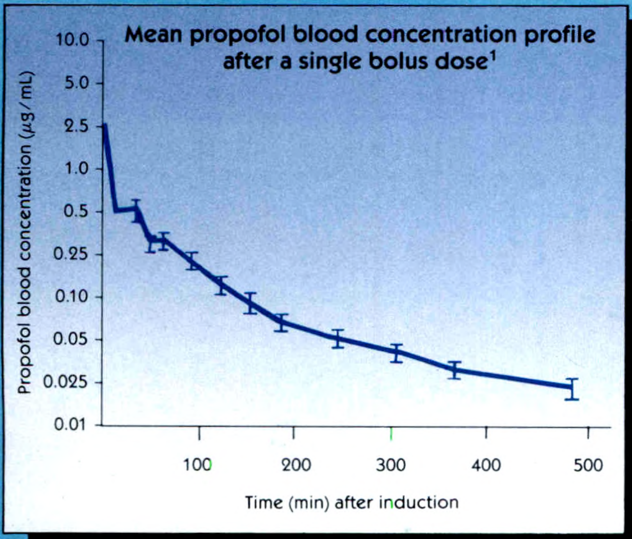
*As with most anesthetic agents, the clearance rate of DIPRIVAN decreases in elderly patients.



—adapted from Cockshott, p 46[1]

DIPRIVAN clearance
5-10 times faster **than barbiturates**

	Clearance rate (L/min)[†]
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thiopental[3]	.11–.30
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[†] Calculations of clearance rates based on 70-kg patient.
—adapted from Way and Trevor, p 803[3]

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Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Eyes open spontaneously	4.0*	6.3
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
Able to stand unassisted	68	87
Able to walk unassisted	70	96
Able to void	102*	173
"Ready" for home	138*	206

*Statistically significant ($P < 0.05$).
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With less of the nausea and vomiting associated with other anesthetic agents—up to 24 hours postop

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Improved speed and quality of recovery compared with thiopental/isoflurane:

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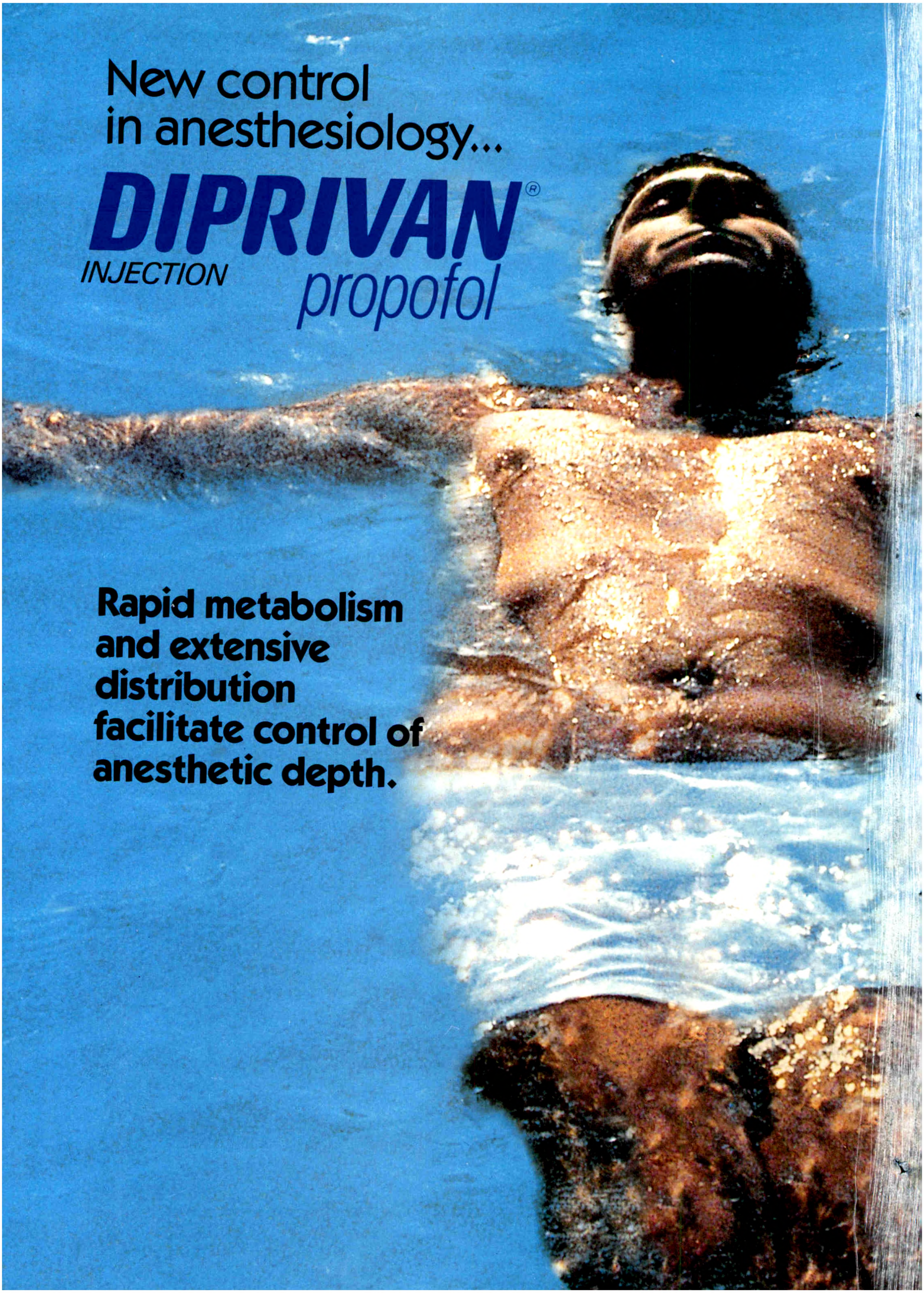
*An adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia.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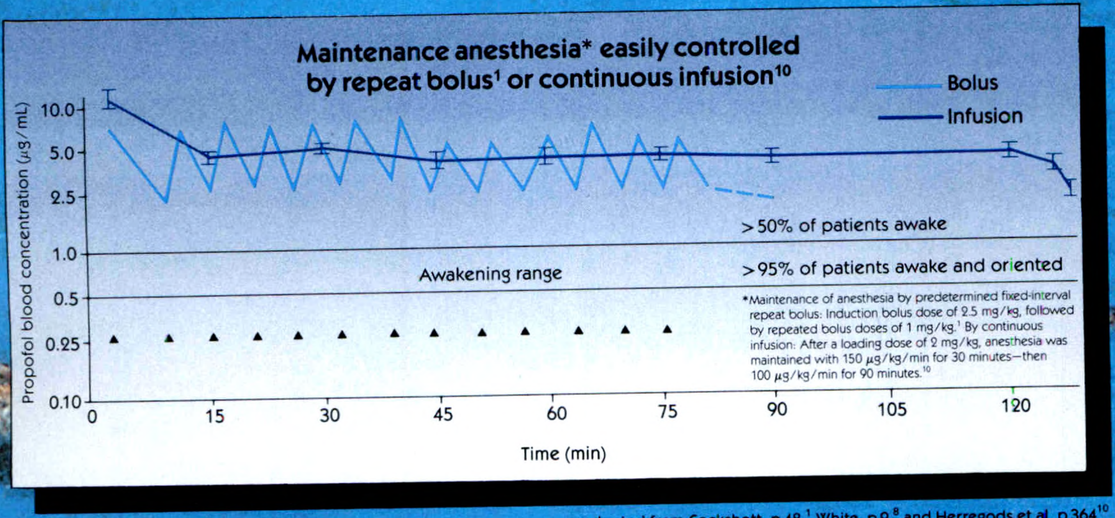
and extensive
distribution
facilitate control of
anesthetic depth.

Maintenance of anesthesia: easily controlled


Maintenance anesthesia* easily controlled by repeat bolus[1] or continuous infusion[10]

*Maintenance of anesthesia by predetermined fixed-interval repeat bolus: Induction bolus dose of 2.5 mg/kg, followed by repeated bolus doses of 1 mg/kg.[1] By continuous infusion: After a loading dose of 2 mg/kg, anesthesia was maintained with 150 μg/kg/min for 30 minutes—then 100 μg/kg/min for 90 minutes.[10]

—adapted from Cockshott, p 48,[1] White, p 9,[8] and Herregods et al, p 364[10]

No reported awareness during maintenance with DIPRIVAN

Overall quality of maintenance anesthesia superior to thiopental/isoflurane.[11]

Assessment of maintenance*[11]

	Excellent	Good	Poor
DIPRIVAN (n = 50)	58%	30%	12%
Thiopental + isoflurane (n = 50)	36%	32%	32%

*Statistically significant differences between all treatment groups ($P < 0.05$, Mantel-Haenszel Test)—as measured by the percent variation from baseline in hemodynamic parameters.

—adapted from Weingarten and Youngberg, data on file[11]

When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

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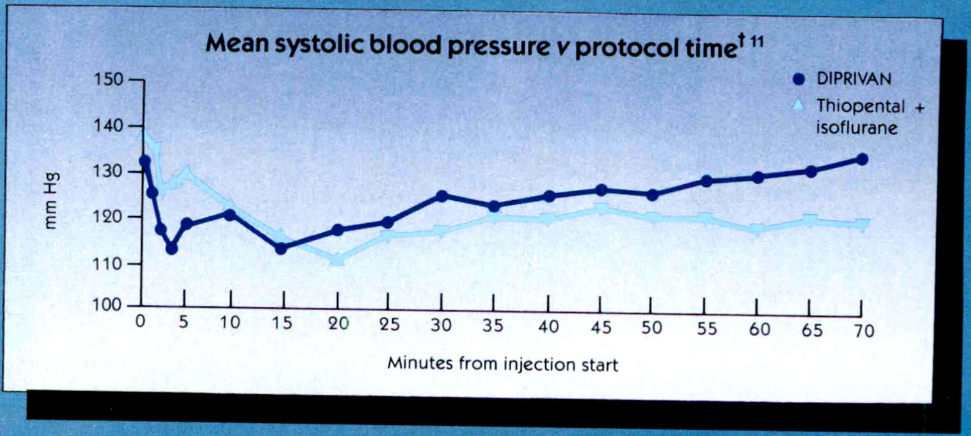
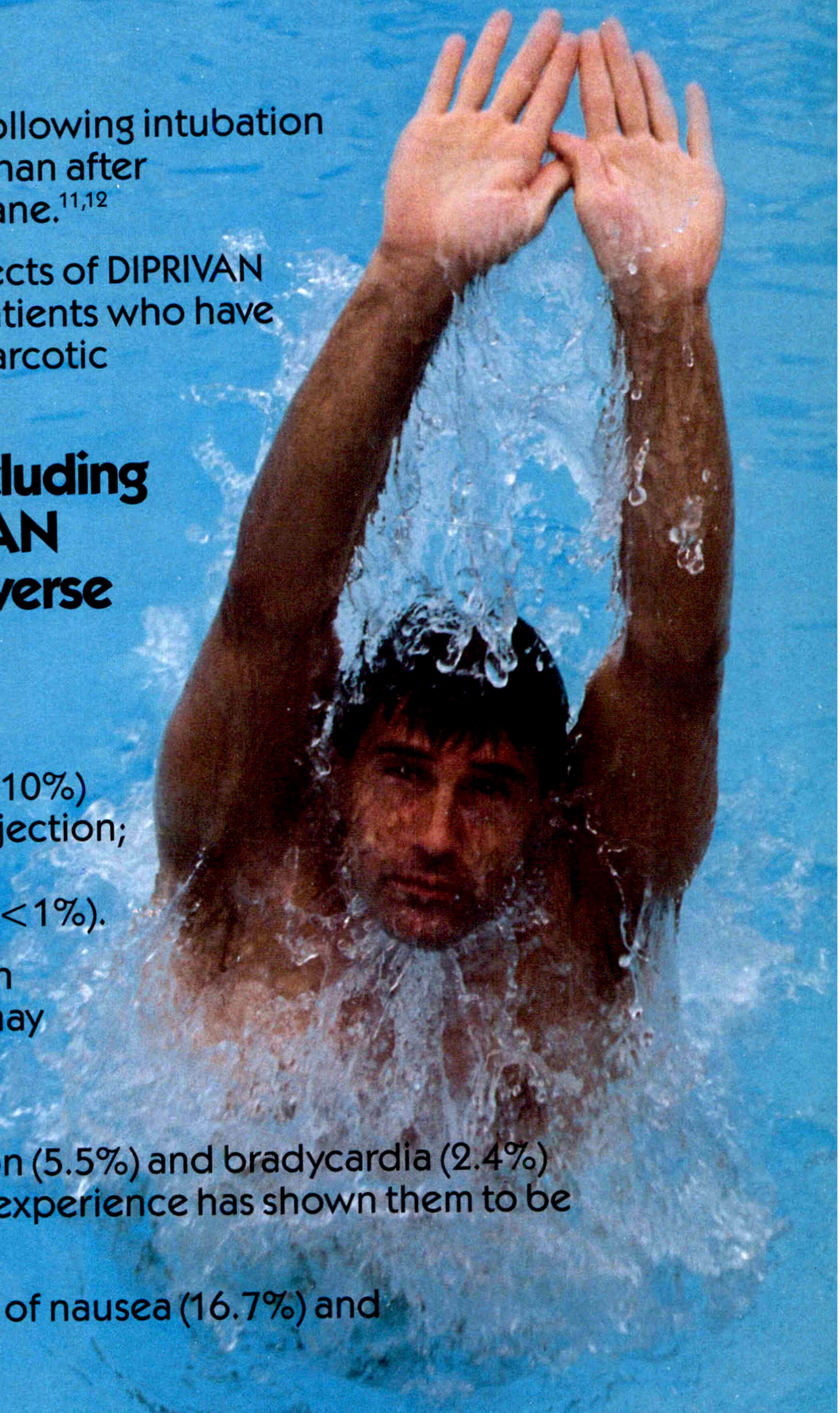


—adapted from Weingarten and Youngberg, data on file[11]

[†] Induction bolus dose: Patients received either DIPRIVAN 2.5 mg/kg or thiopental 5.0 mg/kg. DIPRIVAN patients were then maintained with repeated injections of 25% of the original induction dose supplemented with 60% to 70% nitrous oxide in oxygen. Thiopental/isoflurane patients were maintained with 0.2% to 2.0% isoflurane supplemented with 60% to 70% nitrous oxide in oxygen.[11]

* Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.



- Increase in heart rate following intubation was less pronounced than after thiopental with isoflurane.[11,12]
- The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.*

In clinical trials including over 1500 DIPRIVAN patients, most adverse events were mild and transient

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- Apnea often occurs on induction (43%) and may persist for more than 60 seconds.
- Significant hypotension (5.5%) and bradycardia (2.4%) have been reported†; experience has shown them to be clinically manageable.
- Low overall incidence of nausea (16.7%) and vomiting (9.1%).

*Induction dose requirements may be reduced.

†Sufficient to require intervention.

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DIPRIVAN should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN should be used with caution in elderly, debilitated, and/or hypovolemic patients, and those rated ASA Class III or IV.

DIPRIVAN is not recommended at this time for use in pediatric patients, nursing mothers, patients with increased intracranial pressure or impaired cerebral circulation, and in obstetrics, including cesarean section deliveries.

- DIPRIVAN can be combined with other commonly used agents in anesthesia.
- Also eliminates concerns about operating room/recovery room pollution associated with volatile agents.

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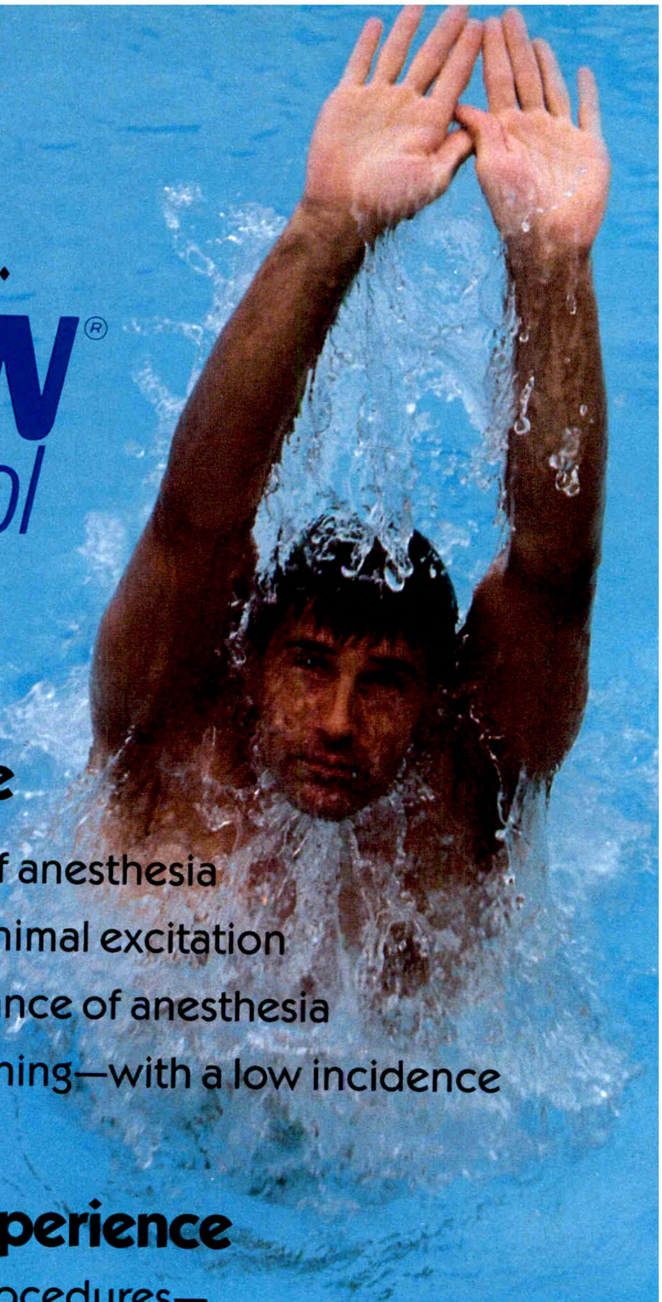

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Extensive worldwide experience

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As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

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WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with l5 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.)*

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.)*

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents.

The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

HOW SUPPLIED: DIPRIVAN Injection (NDC 0038-0290) is available in ready-to-use 20-mL ampules containing 10 mg/mL of propofol.

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

Rev. Q 10/89

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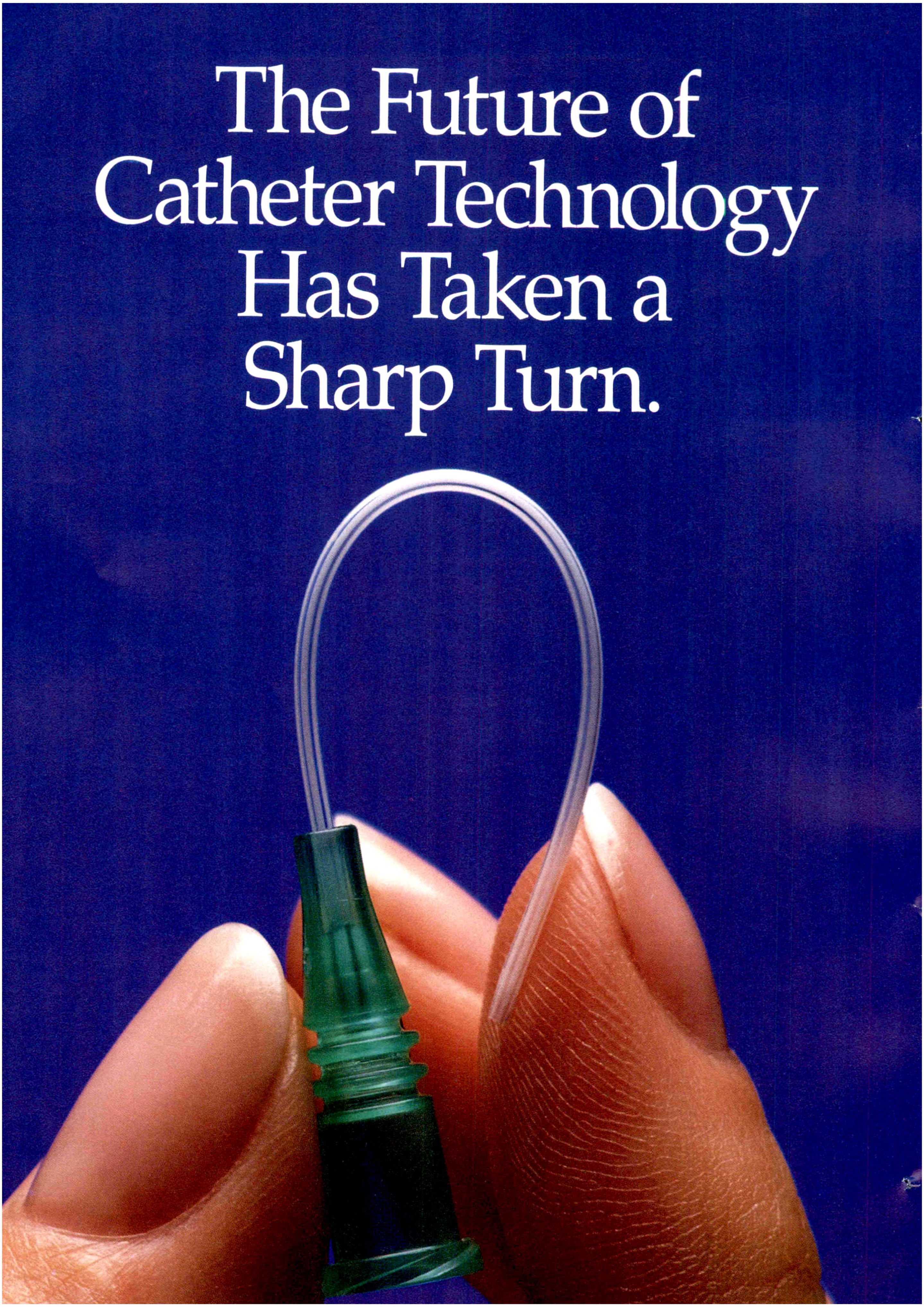
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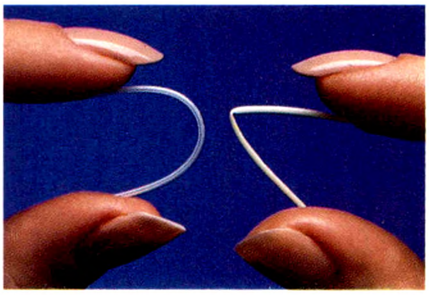

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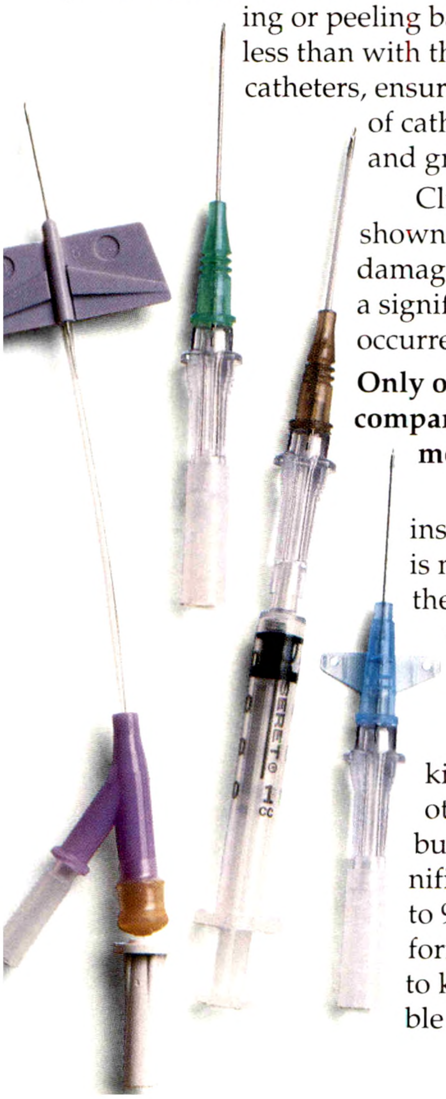

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†P.B. Gaukroger, J.G. Roberts and T. Manners "Infusion Thrombophlebitis: A Prospective comparison of 645 VIALON and Teflon Cannulae in Anesthesia and Postoperative Use." (Department of Anaesthesia and Intensive Care, Finders Medical centre, Adelaide, Australia)

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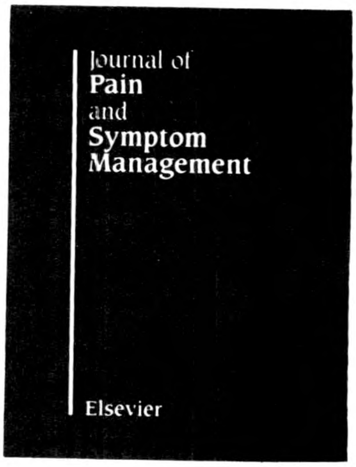
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*Nondepolarizing neuromuscular blocking agents.

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(atracurium besylate)

References and brief summary of full prescribing information can be found on the following page.

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(atracurium besylate)

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Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: **General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: **Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

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Rectal Methohexital: Concentration and Length of the Rectal Catheters

Samia N. Khalil, MD, F. Barry Florence, MD, M.C.O. Van den Nieuwenhuyzen, MS, Alan H. B. Wu, PhD, and T. H. Stanley, MD

KHALIL SN, FLORENCE FB, VAN DEN NIEUWENHUYZEN MCO, WU AHB, STANLEY TH. Rectal methohexital: concentration and length of the rectal catheters. Anesth Analg 1990;70:645–9.

In the study, the authors evaluated the concentration of rectal methohexital (1% vs 10%) and the length of the rectal catheter (3.8 vs 12.7 cm), on sleep-success rate, administration-sleep time, methohexital plasma concentrations, and recovery time in 85 healthy children scheduled for elective ophthalmic or ear, nose, or throat operations lasting approximately 1 h. At a dose of 25 mg/kg, the 1% solution of rectal methohexital was associated with a significant ($P <$ 0.05) higher sleep-success rate (95% vs 70%), shorter administration-sleep time (5.7 ± 1.9 vs 7.0 ± 2.0 min), higher methohexital plasma concentrations at 20 min (6.5 vs 4.7 ng/mL) and at 30 min (5.3 vs 3.7 ng/mL), and prolonged recovery time (53.2 ± 31.1 vs 32.4 ± 18.5 min). The length of the rectal catheters did not significantly affect sleep-success rate, administration-sleep time, methohexital plasma concentrations, or recovery time. The use of 25 mg/kg of 1% rectal methohexital solution to induce anesthesia in children is superior to the use of 25 mg/kg of 10% methohexital solution for induction of anesthesia in children, particularly in operations 1 h or longer in duration.

Key Words: ANESTHETIC TECHNIQUES, RECTAL—methohexital. ANESTHETICS, RECTAL—methohexital.

Rectal methohexital has been used as an induction agent for children with variable success (1,2). Only 84% of children fell asleep within 15 min after 25 mg/kg of 10% methohexital solution (1). The mean administration-sleep time (i.e., the time from methohexital administration until the onset of sleep) in that study was 8.3 ± 3.6 min. The lengths of the rectal catheters were not specified. A previous study in this institution demonstrated that by diluting the methohexital solution to 1% instead of 2% and administering 25 mg/kg with 12.7-cm (5-in.) catheters, the sleep-success rate (i.e., the percentage of the children who fell asleep within 15 min) increased to 98%, and the mean administration-sleep time shortened to 6.2 ± 1 min (3). Our results did not clarify whether the increase in success rate and shortened sleep time was due to dilution of methohexital, to the use of a longer catheter, or to both. The objectives of this study were to evaluate the effect of methohexital concentration (1% vs 10%) and the effect of the length of the rectal catheter (3.8 cm [1.5 in.] vs 12.7 cm [5 in.]) on sleep-success rate, the administration-sleep time, recovery time, and plasma methohexital concentrations.

Methods

Approval was received from the University Human Institutional Review Board, and consent was obtained from the parents of 85 ASA physical status I and II children, aged 1–5 yr, scheduled for elective ophthalmic or ear, nose, or throat operations approximately 1 h in duration. The children were fasting and received no premedication. They were randomly assigned to one of four groups according to concentration of methohexital and length of administration catheter (Table 1).

The children, accompanied by their parents, were brought to the preoperative holding area adjacent to the operating room. While each child was being comforted by the parents, he or she was placed in the

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Table 1. Study Groups

Group	Dose of methohexital (mg/kg)	Concentration of methohexital solution (%)	Length of catheter (cm)
1	25	10	12.7
2	25	10	3.8
3	25	1	12.7
4	25	1	3.8

left lateral position and methohexital was administered via lubricated soft 12.7 cm (5 in.) or 3.8 cm (1.5 in.) long 14F suction catheters, each with one hole at the tip. The whole lengths of the catheters were introduced through the rectum, and the catheters were removed after injection of the methohexital. The methohexital solutions were prepared by a pharmacist using sterile water as a solvent. Each child was monitored with a pulse oximeter and was continuously observed by an anesthesiologist unaware of the group allocation. Sleep was defined as loss of consciousness, lack of response to verbal stimuli, and absence of voluntary movement when unstimulated. If a child did not fall asleep within 15 min, the methohexital dose was considered inadequate and the child was removed from the administration-sleep time analysis. Children were not removed from the study if they defecated. After falling asleep, the children were transported, while lying on their sides and monitored by a pulse oximeter, to the operating room. Decreases in O_2 saturation (Spo_2) below 90%, bradycardia, defecation, vomiting, laryngospasm, complaint of rectal pain or itch, or development of jerky, abnormal muscle movements were recorded.

In the operating room, anesthesia was continued with halothane (0.25%–3.0%) and N_2O (60%) in O_2 via a face mask. Additional monitors included a precordial stethoscope, automated blood pressure (Dinamap), electrocardiogram, temperature probe, and end-tidal CO_2 (mass spectrometry; Perkin Elmer). An intravenous catheter was then inserted into a peripheral vein. Atropine sulfate (0.02 mg/kg) was given intravenously, and orotracheal intubation was facilitated by the use of succinylcholine (1 mg/kg IV). Ventilation was mechanically controlled to keep end-tidal CO_2 at 4%. No opiates, antiemetics, or intravenous anesthetics were used. Blood samples from a peripheral vein were collected 15, 20, 30, 45, and 60 min after methohexital administration in the operating room, and at recovery time in the recovery room. We elected not to draw blood samples before the children were asleep. At the end of the operation, halothane and N_2O were discontinued, the stomach was decompressed, and the trachea was extubated and each child regained protective airway reflexes. The child was then transferred to the recovery room, while lying in the lateral position breathing room air, and monitored by a pulse oximeter. Decreases in Spo_2 below 90% (noted on the way to the recovery room) were recorded.

Postoperative recovery time was assessed by a recovery room nurse, using Steward's simplified postanesthetic recovery score (4). Evaluations were made at 5, 15, 30, 45, and 60 min after admission to the recovery room. Recovery time was defined as the period between termination of all inhalation anesthetics and the time when the child was fully awake, could cough or cry, and moved purposefully.

Plasma methohexital levels were measured using reverse-phase, high-pressure liquid chromatography. The serum proteins were precipitated by adding 100 μL of high-performance liquid chromatography-grade acetonitrile to 100 μL of sample. The mixture was spun for 10 s and centrifuged. One hundred microliters of the extract was injected into a C_{18} column (Waters Associates, Inc., Milford, Mass.), mobile phase 40% acetonitrile and 10% monobasic phosphate buffer, flow rate 1.0 mL/min, and detection at 214 nm. The precision and sensitivity of the assay were 5% and 0.5 μg/mL, respectively.

Statistical Methods

The sleep-success rate was evaluated using the χ^2 test and Fisher's exact tests. The administration-sleep times and recovery times were analyzed using two-way analysis of variance. The mean plasma methohexital concentrations were compared between the groups using two-way analysis of variance. The incidence of bradycardia, defecation, vomiting, hiccoughing, laryngospasm, decrease in Spo_2 below 90%, complaint of rectal pain or itch, and jerky abnormal muscle movements was evaluated using the χ^2 test. Data were reported as mean ± SD; $P \leq 0.05$ was considered statistically significant.

Results

Five of the 85 children who were entered in the study were excluded from analysis: one because an opiate was given intraoperatively and four because they were anesthetized for more than 2 h. Blood samples to measure plasma methohexital concentrations were drawn from only 40 children because funds for additional analyses were not available.

The groups were similar (Table 2) with respect to

Table 2. Demographic Data in the 80 Children Included in the Study

	Group 1	Group 2	Group 3	Group 4
Age (yr)	3.3 ± 1.4	3.1 ± 1.4	3.5 ± 1.4	3.6 ± 1.5
Weight (kg)	15.2 ± 3.6	15.5 ± 3.8	15.8 ± 3.8	15.6 ± 3.9
Height (in.)	37.7 ± 4.4	35.1 ± 8.5	33.4 ± 12.3	29.5 ± 15.9
Duration of anesthesia (min)	61.3 ± 21.6	66.5 ± 42.1	62.9 ± 24.8	61.7 ± 15.9
Duration of surgery (min)	36.0 ± 12.8	37.21 ± 34.4	39.1 ± 23.1	38.2 ± 16.1

Values are mean ± SD.

Table 3. Sleep-Success Rate as a Function of Concentration of Administered Methohexital and Length of the Rectal Catheter in 80 Pediatric Patients

	Total *n*	No. of patients who went to sleep in 15 min	Sleep success rate (%)
Methohexital concentration			
1%	40	38	95
10%	40	28	70[a]
Length of administration catheter (in.)			
3.8 cm	40	33	82.5
12.7 cm	40	33	82.5

[a] Significant ($P < 0.003$).

Table 4. Plasma Methohexital Concentrations (ng/mL)

Time from methohexital administration (min)	Group 1	Group 2	Group 3	Group 4
15	7.7 ± 1.4	5.6 ± 2.5	6.9 ± 2.7	7.9 ± 2.6
20	4.7 ± 2.4	4.8 ± 2.2	6.5 ± 2.4	6.7 ± 2.9
30	4.1 ± 2.3	3.3 ± 1.4	4.9 ± 2.8	5.5 ± 2.6
45	3.4 ± 1.6	2.9 ± 1.7	4.1 ± 2	4.4 ± 2.3
60	2.7 ± 1.3	2.1 ± 1.4	2.8 ± 1.2	3.4 ± 1.9
At recovery	2.7 ± 1.5	1.5 ± 1.3	2.6 ± 1.6	2.2 ± 1.3

At 20 min, the plasma methohexital concentrations were significantly higher ($P < 0.028$) in groups 3 and 4 compared with groups 1 and 2. At 30 min, the plasma methohexital concentrations were significantly higher ($P < 0.048$) in groups 3 and 4 compared with groups 1 and 2.

age, weight, duration of surgery, and duration of anesthesia (time from methohexital administration till the end of inhalation anesthesia). The subgroups from which blood samples were drawn were also similar to each other with respect to age, weight, duration of surgery, and duration of anesthesia.

The sleep-success rate (Table 3) was significantly higher (95%) with 1% methohexital solution ($P < 0.003$) than 10% solution (70%). The sleep-success rate (82.5%) was the same with both the 3.8- and 12.7-cm rectal catheters.

The mean administration-sleep time with 1% methohexital solution was (5.7 ± 1.9 min), which was significantly ($P < 0.008$) shorter than with 10% methohexital solution (7 ± 2.0 min). The mean administration-sleep time with the 3.8-cm catheter (6.6 ± 1.9 min) did not differ significantly from that with the 12.7-cm catheter (5.9 ± 2.1 min).

The methohexital plasma concentrations (Table 4; Figure 1) were significantly higher with 1% methohexital solutions at 20 min ($P < 0.028$) than with 10% methohexital. The methohexital plasma concentrations were also significantly higher at 30 min ($P < 0.048$) with 1% methohexital solutions compared with 10% methohexital solutions. The length of the catheters did not significantly affect methohexital plasma concentration.

The mean recovery time with 1% methohexital solution was 53.2 ± 31.1 min, which was significantly ($P < 0.002$) longer than with the 10% methohexital solution (34.4 ± 18.5 min). The mean recovery time (44.1 ± 18.8 min) after the use of the 12.7-cm catheters did not significantly differ from the recovery time after the use of the 3.8-cm catheters (43.5 ± 25.3 min).

The frequency of defecation with 1% methohexital solution was 27.5%, which was significantly ($P < 0.018$) greater than with 10% methohexital solution (7.5%). None of the children developed a decrease in Spo$_2$ below 90% immediately following methohexital administration, but three children in group 4 had a decrease in Spo$_2$ below 90% upon arrival in the recovery room. The incidence of decreased Spo$_2$ in group 4 was statistically greater ($P < 0.025$) than in the other three groups. None of the children developed bradycardia (heart rate less than 70 beats/min). Only one child in group 4 developed a hiccough after methohexital administration. Three children, in different groups, developed laryngospasm immediately after extubation; this cleared with positive pressure ventilation. None of the children vomited or developed abnormal jerky muscle movements that are sometimes seen after intravenous administration of methohexital. None of the children complained of rectal pain or itching.

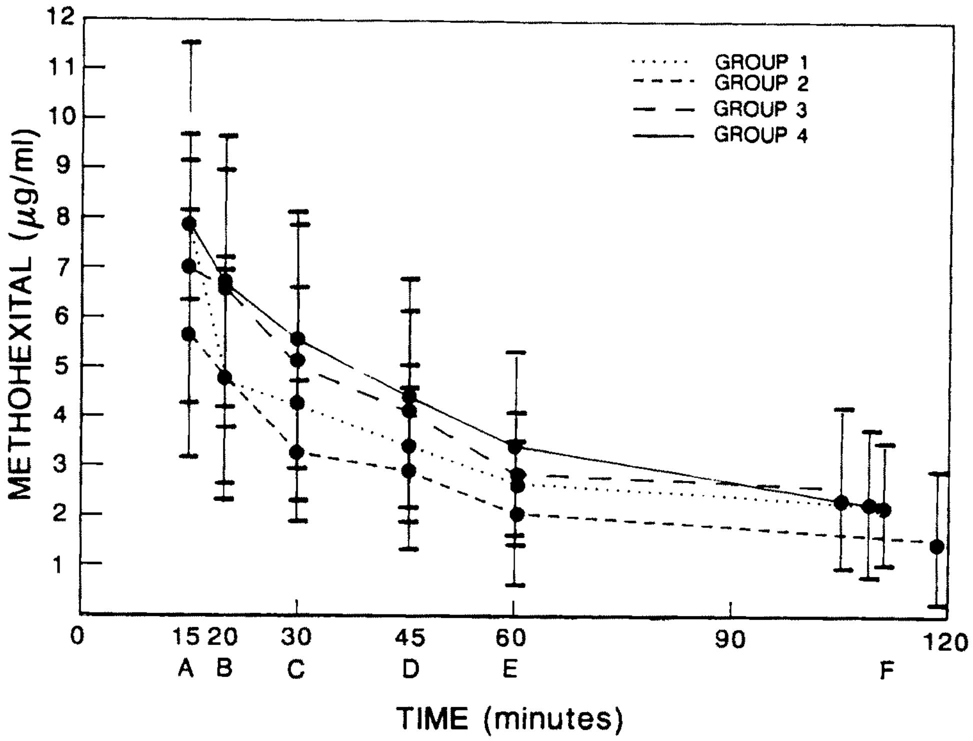

Figure 1. Plasma methohexital concentration. The points in each group represent the mean plasma methohexital concentrations ± SD at 15 (A), 20 (B), 30 (C), 45 (D), 60 (E) min, and at the moment of recovery (F), at which the children reached a Steward recovery score of 6. All of the children in each of the four groups received 25 mg/kg of methohexital. In group 1, the concentration of methohexital was 10% and the catheter was 12.7 cm long; in group 2, the concentration of methohexital was 10% and the catheter was 3.8 cm long; in group 3, the concentration of the solution was 1% and the catheter was 12.7 cm long; and in group 4, the concentration of the solution was 1% and the catheter was 3.8 cm long.

Discussion

This study documents that systemic absorption of rectal methohexital is enhanced by diluting the methohexital solution to 1%. The large volume of the dilute solution exposes a larger surface area of the sigmoidorectal mucosa to the drug, which probably facilitates absorption; as a result, patients receiving 1% methohexital had higher plasma methohexital concentration, higher sleep-success rates, shorter administration-sleep times, and a more prolonged recovery. In our study, only 70% of the children who received the 10% methohexital solution were asleep after 15 min. In the study by Liu et al. using 25 mg/kg of 10% methohexital solution, 84% of the children went to sleep in 15 min (1). In that study, the dose of methohexital had to be increased by 20% (i.e., to 30 mg/kg of the 10% solution) to increase the sleep-success rate to 93%. Also, in the second study by Liu et al. using 25 mg/kg of 10% solution, the sleep-success rate was 85% (5), whereas in Goresky and Steward's study using a similar dose and concentration, the sleep success rate was 92% (2). We cannot be sure of the explanation for the difference in the success rate after using 25 mg/kg of 10% methohexital solution, but the difference may indicate less reliability and variable absorption of the concentrated methohexital solutions, leading to unpredictable results.

The plasma methohexital levels were higher after the use of 1% methohexital solution than after 10% solution, indicating better absorption. In our study, the plasma methohexital levels at recovery times support Dr. Liu's study that "children are likely to fall asleep if the plasma methohexital concentration is above 2 µg/mL" (5). Also, the peak plasma methohexital concentrations in both studies by Liu et al. and in our study are quite similar.

As recovery time in the present study was significantly longer after the use of 25 mg/kg of 1% methohexital solution than after 25 mg/kg of 10% solution, the use of 25 mg/kg of 1% methohexital solution may not be appropriate before operations lasting less than 1 h. A study is needed to evaluate whether a dose less than 25 mg/kg of 1% methohexital solution will be sufficient to achieve a high success rate without prolongation of recovery.

The length of the catheters for rectal administration of methohexital did not significantly affect the sleep-success rates, administration-sleep times, plasma methohexital concentrations, or recovery times. It has been previously recommended that rectal medications should be deposited into the lower third of the rectum (6) to avoid drug absorption into the portal venous circulation with subsequent first-pass hepatic metabolism and decreased bioavailability (7). In our study there were no significant differences between the groups having methohexital administered with long or short catheters. This may be due to anastomosis of the blood supply between the sigmoid and the rectum, which supports the hypothesis that most drugs placed in lower, middle, or upper thirds of the rectum will pass via the hepatic portal vein to the liver and so the first-pass effect is not avoided by use of short catheters (8).

Our study demonstrates the effectiveness and the safety of using 25 mg/kg of 1% methohexital solution. None of the children in our study experienced a clinical cardiorespiratory depression or a decrease in Spo_2 below 90% following methohexital administration. Still, when rectal methohexital is administered to children, they should be under the supervision of an anesthesiologist and the proper equipment and drugs for airway management should be at hand.

As four children in group 4 developed an Spo_2 below 90% on arrival at the recovery room that could be related to an interaction between elevated plasma methohexital concentration and residual halothane, administering oxygen to children while being transported to the recovery room is recommended.

In conclusion, the use of 25 mg/kg of 1% rectal methohexital is associated with better systemic absorption of the same amount of methohexital given as a 10% solution as evidenced by higher sleep-success rates, more rapid onset, higher plasma concentrations, and longer recovery time.

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Subjective Responses to Train-of-Four and Double Burst Stimulation in Awake Patients

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CONNELLY NR, SILVERMAN DG, O'CONNOR TZ, BRULL SJ. Subjective responses to train-of-four and double burst stimulation in awake patients. Anesth Analg 1990;70:650–3.

The present study was undertaken to determine whether the discomfort associated with the sequential bursts of stimuli comprising the two recommended forms of double burst stimulation (DBS) is comparable to that associated with the repetitive stimuli of train-of-four (TOF). Twenty-one unmedicated volunteers rated on a visual analog scale the discomfort associated with randomly applied DBS and TOF stimulations at 20, 30 and 50 mA. All participants were blinded to the mode of stimulation, as well as to the current intensity. At each amperage tested, TOF produced significantly less discomfort than either form of DBS ($P < 0.01$). Stimulation at 50 mA produced median visual analog scale scores of 7.5, 7.0, and 5.0 for $DBS_{3,2}$, $DBS_{3,3}$, and TOF, respectively. At 30 mA the corresponding median visual analog scale scores were 4.5, 5.5, and 3.0, whereas at 20 mA the scores were 4.0, 4.5, and 2.0, respectively. Thus, DBS is more uncomfortable than TOF at each current tested; however, in light of reports of its higher sensitivity, DBS may be the preferred means of assessing neuromuscular function in the awake as well as the anesthetized patient when a force transducer and recorder are not readily available.

Key Words: MEASUREMENT TECHNIQUES, NEUROMUSCULAR—train-of-four, double burst stimulation. NEUROMUSCULAR TRANSMISSION, MEASUREMENTS—train-of-four, double burst stimulation.

The detection of residual neuromuscular blockade in the postoperative patient presents a challenge to the anesthesiologist because the patient frequently is not awake enough to cooperate with clinical testing, yet is awake enough to experience the discomfort associated with nerve stimulation (1). Neuromuscular monitoring is used to guide intraoperative administration of neuromuscular blocking drugs, and also to test postoperative return of neuromuscular function (2–4). The measurement of neuromuscular function in the postoperative patient who may be experiencing residual blockade would be facilitated by a simple, painless means of neurostimulation that would not require quantification of responses with a force transducer interfaced with a recorder (e.g., adductor pollicis monitor). Visual and/or tactile evaluation of fade in response to train-of-four (TOF) stimulation typically is not sensitive enough for detection of residual neuromuscular blockade (5). Although the neuromuscular response to a tetanic stimulus is more discernible, such a stimulus is very uncomfortable (2) and generally is not applied to awake patients.

Double burst stimulation (DBS) recently has been introduced in an effort to improve tactile and visual detection of fade, and thus obviate the need for a 5-s tetanus (5,6). Double burst stimulation consists of two high-frequency (50 Hz) bursts of stimuli separated by 750 ms. Each burst contains two or three individual stimuli, depending on the stimulation mode; thus, $DBS_{3,3}$ incorporates two groups of three stimuli each, whereas only two stimuli are incorporated in the second group of the $DBS_{3,2}$ (Figure 1). Because DBS is more sensitive than TOF in the visual and/or tactile evaluation of fade (5,6), it might be a more useful method of evaluating the awake patient in whom residual blockade is suspected. We undertook the present study in awake volunteers to evaluate whether this clinically more sensitive means of assessment would be tolerated as well as TOF mon-

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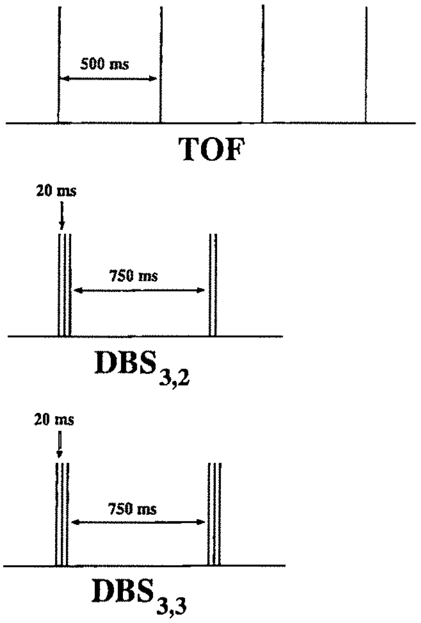

Figure 1. Illustration of train-of-four (TOF) and double burst stimulation (DBS). All stimuli are 200 μs in duration, square-wave pattern, and of equal current intensity. Train-of-four consists of four such stimuli at a frequency of 2 Hz. $DBS_{3,2}$ consists of three stimuli at 50 Hz followed 750 ms later by a burst of two stimuli at 50 Hz. $DBS_{3,3}$ consists of two groups of three stimuli at 50 Hz separated by 750 ms.

itoring, and whether submaximal stimulating currents delivered by the neuromuscular testing units would reduce discomfort.

Methods

The protocol was approved by the institutional human investigation committee. Twenty-one unmedicated volunteers, aged 22–70 yr and free of known neuromuscular disease, were evaluated. Verbal informed consent was obtained from each volunteer before the evaluation, and each of them was instructed on the use of a visual analog scale (VAS). The ulnar nerve was stimulated via cutaneous electrodes with a calibrated Myotest DBS (Biometer, Denmark) nerve stimulator. The positive electrode was placed over the olecranon groove, and the negative electrode was placed on the volar aspect of the forearm. Before VAS testing, the Myotest DBS output was measured on an oscilloscope (Tektronix 7623A, Tektronix Inc, Beaverton, Ore.) to confirm consistent current output over its range (in 10-mA increments) in all three modes of neuromuscular stimulation (i.e., TOF, $DBS_{3,2}$, and $DBS_{3,3}$). All stimuli delivered were 200 μs in duration. Train-of-four, $DBS_{3,2}$, and $DBS_{3,3}$ stimulations were each delivered at 20, 30, and 50 mA, with a 20-s interval between each stimulation. Each volunteer received one of the nine stimuli before actual testing in order to minimize the element of surprise on subsequent testing. The volunteer then received the nine sets of stimuli in random order, being blinded to mode of stimulation and current intensity. Discomfort was rated utilizing a VAS, anchored with no discomfort at 0 and worst discomfort imaginable at 10. A subgroup of five of the original 21 volunteers were reevaluated 1 mo later to determine the reproducibility of the VAS response over time. The data are expressed as median (with 25th–75th percentile range). Differences between the VAS values at the various currents and stimulation patterns were analyzed by the Friedman test and Wilcoxon signed-rank test for nonparametric paired data. Differences were considered statistically significant at the $P < 0.05$ level. When multiple comparisons were made, a Bonferroni adjustment was made to the significance level.

Results

After the first neuromuscular stimulation, one of the individuals elected not to continue the study because of the discomfort associated with it. This participant had received a TOF stimulation at 30 mA. The VAS scores for the individual stimulations in the remaining 20 volunteers are summarized in Figure 2. The median VAS values (with 25th–75th percentile range) for TOF at 50 mA were 5.0 (3.0–6.5). These indicated significantly less ($P < 0.01$) discomfort than was associated with $DBS_{3,2}$ and $DBS_{3,3}$, whose values were 7.5 (5.0–9.0) and 7.0 (6.0–9.0), respectively.

At lower currents (both 20 and 30 mA), TOF was again significantly less uncomfortable ($P < 0.01$) than its DBS counterparts. At 20 mA, the VAS values for TOF were 2.0 (1.0–3.0), whereas those for $DBS_{3,2}$ and $DBS_{3,3}$ were 4.0 (2.8–5.0) and 4.5 (2.5–5.0), respectively. At 30 mA, corresponding values were 3.0 (2.0–4.0), 4.5 (4.0–6.5), and 5.5 (6.0–9.0), respectively.

As amperage increased, TOF became significantly more uncomfortable ($P < 0.01$) with each increment in amperage. Double burst stimulation also became more uncomfortable with each increasing current ($P < 0.01$) for both $DBS_{3,2}$ and $DBS_{3,3}$. The VAS scores for $DBS_{3,3}$ tended to be slightly though not significantly higher than for $DBS_{3,2}$ at each of the three currents tested.

Comparison of TOF at 50 mA to DBS at lesser currents indicated that TOF at 50 mA was more uncomfortable than $DBS_{3,2}$ at 20 mA ($P < 0.05$). However, the VAS values for TOF at 50 mA were not significantly different than those for $DBS_{3,2}$ at 30 mA, $DBS_{3,3}$ at 20 mA, or $DBS_{3,3}$ at 30 mA.

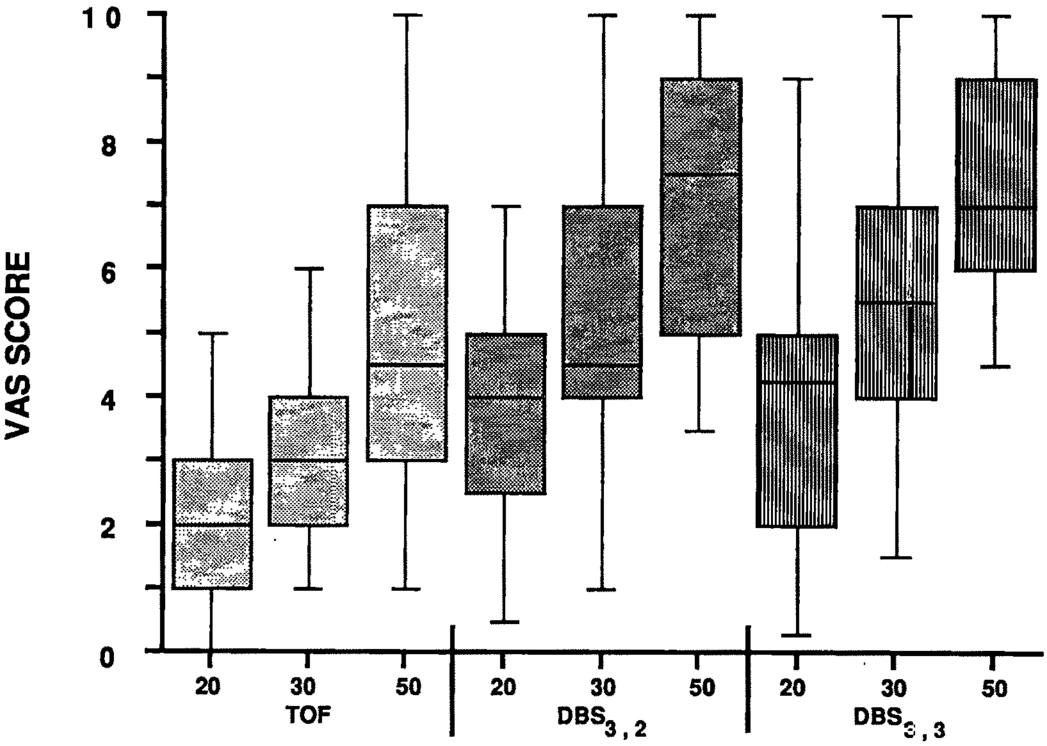

Figure 2. The VAS scores of the different modes of stimulation at the three current amperages. The 25th–75th percentiles are represented by the *shaded areas*. The medians are shown as *horizontal lines* within the shaded areas. The 0–100th percentiles are described by the *extended bars*.

In the subgroup of volunteers who were retested 1 mo later, the individual as well as the median VAS values were consistently lower for TOF than for either $DBS_{3,2}$ or $DBS_{3,3}$. This was true at each of the three amperages tested during both study periods. At both testing periods, decreased currents were associated with decreased discomfort.

Discussion

The goal in developing tests of neuromuscular function in awake patients is to improve sensitivity and clinical usefulness, while minimizing discomfort. Train-of-four monitoring is the most commonly used means of evaluating the degree of neuromuscular blockade. It can be performed on anesthetized as well as awakening patients, is less painful than tetanic stimulation, and requires no preblockade baseline measurement because it serves as its own control (7–9). Its disadvantage is lack of sensitivity when using visual and/or tactile means of assessment (5,6,10), because fade may not be detected even when the TOF ratio is as low as 0.3 (10).

Some authors (7) state that TOF stimulation is a painless means of neuromuscular blockade evaluation. Our data refute this position. Although generally well-tolerated in our study, TOF clearly was not painless: the median VAS value for TOF at 50 mA was 5.0, and one individual discontinued participation in the study because of the discomfort produced by TOF at 30 mA. One approach to a recovering patient in whom weakness was suspected would be to omit neuromuscular testing and its associated discomfort, and simply administer a second dose of the reversal agent. However, side effects of anticholinesterases can occur, and overdosage with these agents is known to potentiate blockade rather than reverse it (11,12). Thus, testing of neuromuscular function still remains valuable in the postoperative patient who is suspected of residual neuromuscular blockade.

Traditionally, sensitivity of testing has been improved by increasing the stress placed on the neuromuscular junction (i.e., increasing the intensity and/or duration of the stimulus) at the expense of increased discomfort in awake patients. The classic example of such a high stress is a 5-s, 50-Hz tetanic stimulation (13). This is a sensitive means of measuring the return of neuromuscular function (9,14,15), but has the disadvantage of being very painful and thus unacceptable to awake patients (2,8,9,16). The administration of two brief tetanic stimuli (as in DBS) avoids the relatively long duration that is typically employed during tetanic stimulation. In the absence of a mechanical recording device, DBS has been reported to provide a more sensitive manual detection of fade than does TOF. Because DBS is a stimulus of a higher frequency than is TOF, it may allow a current of lower intensity, and thus less discomfort, to be employed. It has been shown that when interfaced with an adductor pollicis force transducer, the TOF ratio is comparable at 20, 30, and 50 mA (17). Whether the detection of fade by DBS is as easily accomplished at lower currents (i.e., 20 and 30 mA) as it is at 50 mA remains to be determined. If DBS assessment proves to be equally reliable at submaximal currents, and because it is more sensitive than TOF in manual and/or visual detection of fade, then DBS would be more suitable for use in awake patients. Because disagreement still exists (5,6,18) as to which form of DBS is more clinically useful in tactile evaluation of fade, it is reassuring that at 20 or 30 mA neither $DBS_{3,2}$ nor $DBS_{3,3}$ is more uncomfortable than TOF at 50 mA.

In conclusion, although tolerated by awake participants in the present study, DBS is significantly more uncomfortable than TOF. This is true at each of the amperages studied for both $DBS_{3,2}$ and $DBS_{3,3}$. These results were reproducible, as the rank order of the VAS values in our subgroup of five volunteers remained constant over time. The ideal means of assessing neuromuscular blockade in the awake patient remains to be determined. However, in view of the potential morbidity associated with residual neuromuscular blockade, DBS remains a valuable option in the absence of an adductor pollicis monitor: it avoids a painful tetanic stimulation, while still providing a more sensitive visual and/or tactile means of evaluation than does TOF.

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Technical Communication

A Method for Testing for Epinephrine-Induced Arrhythmias in Rats

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LASTER MJ, JOHNSON BH, EGER EI II, TAHERI S. A method for testing for epinephrine-induced arrhythmias in rats. Anesth Analg 1990;70:654–7.

Evaluation of a new inhaled anesthetic requires determination of the anesthetic's potential to predispose to ventricular (and other) arrhythmias in an animal model. This need poses logistic and economic burdens if the effects of large numbers of new anesthetics are to be surveyed. We have devised a technique for determining the potential of a new anesthetic to produce arrhythmias using a smaller animal (the rat) than previous methods. Our technique requires preliminary selection of male rats sensitive to the arrhythmias produced by the intravenous injection of epinephrine. Rats are tested after demonstrating the desired sensitivity. Using this model, rats given 1.4% halothane developed premature ventricular extrasystoles at a dose of 2.4 ± 1.0 μg/kg epinephrine, and those receiving 1.6%–2.2% isoflurane at a dose of 28 ± 24 μg/kg. This difference in dose requirements is about two to three times that in humans.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHETICS, VOLATILE—halothane. HEART, ARRHYTHMIAS.

The evaluation of a new inhaled anesthetic includes determination in an animal model of the potential to produce arrhythmias, particularly premature ventricular contractions (PVCs), in response to injection of epinephrine. This need poses logistic and economic burdens if the effects of large numbers of new anesthetics are to be surveyed. Large animals such as dogs (1,2), pigs (3), or goats (4) are typically used for this purpose; they are, however, prohibitively expensive for large scale surveys of new agents; moreover, their availability may be limited and their living and study space requirements are considerable. Although smaller animals are widely used to test for arrhythmias, they (as far as we can tell) have not been used to assay the potential of inhaled anesthetics to produce arrhythmias, particularly in the context of injection of epinephrine. Thus, we have developed a method for testing for arrhythmias in the rat.

Methods

Our project was approved by the University of California at San Francisco Committee on Animal Research. In initial studies, we discovered two problems. First, we found a sex-specific difference in the response of Sprague–Dawley rats to the arrhythmic effects of epinephrine. Female rats anesthetized with 1.4% halothane frequently failed to develop PVCs after intravenous bolus injections of doses of 64–128 μg/kg. Second, although more sensitive, not all male rats developed PVCs with injection of epinephrine. Consequently, we screened male rats to verify their susceptibility to epinephrine-induced PVCs (we defined susceptibility as the development of three or more PVCs after intravenous administration of a bolus of 4 μg/kg epinephrine or less) during halothane anesthesia. We then tested the reproducibility of our results on subsequent occasions both on different days and on the same day. We also determined whether the

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subcutaneous injection of a small dose of lidocaine would decrease the dose of epinephrine required to produce PVCs. Note that we tested only for the development of PVCs; we did not test for other ventricular arrhythmias, nor did we test for atrial arrhythmias.

We screened 43 male, Sprague–Dawley, specific-pathogen-free rats (445 ± 65 g) (mean ± SD) obtained from Charles River Laboratories. Four animals usually were tested concurrently. Each animal was weighed, then placed in an individual plastic cylinder and anesthetized with halothane, 1.4% in O_2 delivered using an inflow rate of 4 L/min. An inflow rate of 4 L/min was used to ensure that CO_2 levels were minimized. Carbon dioxide levels were measured using infrared analysis and were maintained below 1.6% (median value 0.8%). Rectal temperature was monitored using thermister probes and maintained at 38.3° ± 0.7°C. Subcutaneous platinum needle electrodes (type E2, Grass Instrument, Quincy, Mass.) were placed in the right and left shoulder and the right thigh and connected to a Grass model 7 polygraph to obtain electrocardiograms. A 24F, 0.75-in. plastic catheter (Deseret Teflon Angiocath) was inserted into the dorsal tail vein to allow injection of epinephrine.

The screening test method consisted of the following. A bolus of epinephrine, 0.25 μg/kg, was injected intravenously and the electrocardiogram was monitored for 60 s. A response of three or more PVCs was considered positive, and no further epinephrine was administered after a positive result was obtained. When two or fewer PVCs occurred, we allowed the rat to recover for at least 30 min, then administered double the dose of epinephrine. Premature ventricular contractions usually were defined by their larger and broader QRS complexes, by the absence of a preceding P wave, and by their irregular position relative to the prior, normal sinus beats. This process was repeated until the rat developed three or more PVCs or had received a dose of 4 μg/kg.

We eliminated from the study 17 rats who failed to develop PVCs and one who developed an enlargement of the submaxillary glands. The data from one rat who died early in the course of the study were also excluded from analysis. The remaining 26 rats were allocated to one or more of three groups. These three groups were used to determine (a) whether the dose of epinephrine required to produce PVCs changed on different days and whether the dose required during halothane anesthesia differed from that required during isoflurane anesthesia, (b) whether the dose required was decreased by the subcutaneous injection of a small amount of lidocaine, and (c) whether the dose required varied as a function of repeated injections on the same day.

In our first study we determined whether the dose of epinephrine required to produce PVCs changed from day to day and whether that dose differed as a function of the anesthetic used. Ten rats were divided into two equal subgroups that were tested at weekly intervals. The first subgroup was given 1.4% halothane the first and second weeks, 1.9% isoflurane the third week, and 2.2% isoflurane the fourth week. The second subgroup received 1.4% halothane the first week, 1.6% isoflurane the second week, 1.4% halothane the third week, and 2.2% isoflurane the fourth week. These doses were chosen because they provide light (i.e., 1.2–1.5 MAC) levels of anesthesia and because the level of anesthesia does not affect the arrhythmic dose of epinephrine (3,5). Rats were tested for arrhythmias using the screening test method with two minor modifications. The first dose of epinephrine injected during halothane anesthesia was immediately less than the dose that had produced PVCs during screening, whereas the first dose injected during isoflurane was the one that had produced PVCs. Injections were made until three or more PVCs appeared or until (isoflurane only) a dose of 16–32 μg/kg had been given. If no PVCs occurred at these higher doses, we assumed that PVCs would have appeared at the next higher dose (32–64 μg/kg). One rat given 32 μg/kg during isoflurane died with ventricular fibrillation. This was the fourth study for this rat, and his data are included.

The doses of epinephrine required to produce three or more PVCs in the minute after injection of epinephrine were compared using paired *t*-tests before and after logarithmic conversion of the data. Logarithmic conversion was performed because of the exponential dose regimen and the skewed nature of the dose-response relationship (i.e., the conversion produced a more normal distribution of values). The first and second epinephrine values obtained for each anesthetic were averaged, then compared, before and after conversion.

In our second study, we measured the effect of local anesthesia on the arrhythmia threshold. We studied 10 rats before and 30 min after the subcutaneous injection of 0.1 mL of 0.5% lidocaine (~1 mg/kg body wt of lidocaine). Rats were anesthetized with halothane using a concentration of 1.4%. The doses of epinephrine required to produce three or more PVCs in the minute after injection of epinephrine were compared using paired *t*-tests before and after logarithmic conversion of the data.

In the third study, we assessed the effect of repeated testing for arrhythmia. We studied eight rats

Table 1. Dose of Epinephrine Producing More Than Two Premature Ventricular Contractions in 1 min: Effect of Anesthetic Choice

	Halothane (μg/kg)		Isoflurane (μg/kg)	
	First administration	Second administration	First administration	Second administration
Unconverted data	2.2 ± 1.1	2.6 ± 1.3	22 ± 24	33 ± 25
Average, doses 1 and 2	2.4 ± 1.0		28 ± 24[a]	
Log, base 10	0.27 ± 0.26	0.36 ± 0.24	1.1 ± 0.5	1.4 ± 0.4[b]
Average, doses 1 and 2	0.33 ± 0.23		1.3 ± 0.4[c]	

All values are expressed as mean ± SD.
[a] $P < 0.02$, compared with halothane.
[b] $P < 0.03$, compared with other isoflurane.
[c] $P < 0.0001$, compared with halothane.

Table 2. Dose of Epinephrine Producing More Than Two Premature Ventricular Contractions in 1 min: Effect of Repeated Administrations on Separate Occasions

	First administration (μg/kg)	Second administration (μg/kg)	Third administration (μg/kg)	Fourth administration (μg/kg)
Unconverted data	2.6 ± 1.5	3.5 ± 2.3	2.9 ± 1.2	2.4 ± 1.5
Log, base 10	0.34 ± 0.34	0.45 ± 0.32	0.41 ± 0.22	0.26 ± 0.41

All values are expressed as mean ± SD.

(four of which had been used in the previous study of lidocaine, but had been tested on a separate day) and determined the arrhythmic threshold four times in succession during the same anesthetic experience. Each occasion (i.e., each testing in quadruplicate) was separated from the previous one by at least 5 days. The first and third determinations were made as described previously. The second and fourth determinations were made by use of the previously determined threshold: for these latter determinations, we chose as the initial dose of epinephrine that dose immediately below the dose that produced PVCs. The doses of epinephrine (with and without logarithmic conversion) required to produce three or more PVCs in the minute after injection of epinephrine were compared using an analysis of variance.

Results

The dose of epinephrine required to produce three or more PVCs during anesthesia with halothane was the same for the first and second administration of halothane before and after logarithmic conversion of the data (Table 1). During isoflurane, these doses of epinephrine did not differ when the unconverted data were compared. After logarithmic conversion, the second dose requirement was significantly higher than the first. The average of the doses of epinephrine eliciting PVCs during halothane was significantly lower than the average for isoflurane, with and without data conversion.

Lidocaine injection did not increase the dose required to produce PVCs. The dose before injection was 2.7 ± 1.3 mg/kg and after injection it was 4.7 ± 9.1 mg/kg. After logarithmic conversion the respective values were 0.36 ± 0.30 mg/kg versus 0.36 ± 0.44 mg/kg.

No consistent change appeared in the threshold for arrhythmia in animals tested on four separate occasions (Table 2). Analysis of variance did not reveal a significant difference before or after logarithmic conversion. Furthermore, paired analysis of the first threshold value did not differ significantly from the threshold found with any of the subsequent values with or without logarithmic conversion.

Discussion

Our results indicate that the rat can be used to investigate the potential of a new inhaled anesthetic to predispose recipients to arrhythmias, particularly to premature ventricular contraction. The dose of epinephrine (2–4 μg/kg) that produced premature ventricular contractions in the presence of halothane in our model is close to that producing this reaction in humans given a submucosal injection of epinephrine (2.1 μg/kg) during halothane anesthesia (6). The significantly higher epinephrine dose requirement during isoflurane is consistent with studies in larger animals (1). The difference in the epinephrine dose requirement in rats undergoing halothane and isoflurane anesthesia (an 8.8-fold difference) is greater than that apparent in humans (3.2-fold) (6), suggesting that our rat model may be a more sensitive indicator of arrhythmias than the human model.

Because future investigators may wish to provide local anesthesia for studies of arrhythmias in awake animals, we tested whether a small dose of subcutaneous lidocaine would alter the arrhythmic dose. Our data suggest that injection of 1 mg/kg of lidocaine 30 min before the determination of the arrhythmic threshold should not affect the arrhythmic dose of epinephrine. This result may appear to differ from that found by Johnston et al. (6) in humans, but the difference may be readily explained. The dose of lidocaine we used was smaller (1 versus 3.7 mg/kg). The vascularity of the skin is probably less than that of the mucous membranes used in the Johnston study and thus, in their study, the absorption of lidocaine would be more rapid and would occur at a time more proximate to the injection of epinephrine. Proximity to the injection of epinephrine also differed in our study in that we waited 30 min before beginning our challenge with epinephrine.

There may be, however, a small limitation to the model we have devised. The second test of epinephrine-induced arrhythmias during isoflurane was associated with a small but significant increase in epinephrine dose requirement. This trend was inconsistent during halothane anesthesia.

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Clinical Reports

Continuous Microcatheter Spinal Anesthesia With Subarachnoid Meperidine for Labor and Delivery

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Key Words: ANALGESICS, MEPERIDINE.
ANESTHETIC TECHNIQUES, SPINAL—meperidine.
ALLERGY, LOCAL ANESTHETICS.

Meperidine has been reported to have local anesthetic activity separate from its narcotic receptor agonist effect (1,2). We describe the use of high-dose subarachnoid meperidine as the sole agent for continuous spinal anesthesia for labor and delivery in a patient presumed allergic to local anesthetics.

Case Report

The patient was a 28-yr-old, white, gravida 1 para 0, 176.3-cm, 73.8-kg woman who was seen in consultation at 38 wk gestation because of a history of "allergy to local anesthetics." She had a history of mild asthma since childhood for which she used a metaproterenol inhaler as necessary, but had never been admitted to a hospital for treatment of asthma. She reported allergies to povidone-iodine solution, tetracycline, erythromycin, lidocaine, and "Novocaine" manifested by rash and urticaria. In addition, she reported an extrapyramidal reaction to proclorperazine. Six months earlier she had suffered an apparent allergic reaction in a dentist's office when given a maxillary injection of local anesthetic. She developed a rash and hives on her neck, face, arms, and trunk that subsided after several hours. The agent used was described as "Novocaine." The specific local anesthetic agent and the presence or absence of preservatives could not be confirmed. At 33 wk gestation, the patient presented to the emergency room with severe dehydration secondary to viral gastroenteritis. When local infiltration with 1% lidocaine was used for insertion of an intravenous (IV) catheter, she immediately developed a rash at the IV site, which proceeded to include her face, neck, arms, chest, back, and upper abdomen, and which was also associated with mild wheezing. She was treated with 50 mg of IV diphenhydramine and her symptoms resolved over the next several hours.

Emergency room personnel reported that single-dose, preservative-free 1% lidocaine ampules are usually used for IV placement, but multidose vials containing preservatives are also available and their use could not be ruled out in this case. Because a serious allergic reaction to a skin test at the time of consultation would place mother and fetus at risk, we considered the risk of an allergic reaction associated with skin testing to be unacceptable then or during the remainder of the pregnancy. In addition, the efficacy and sensitivity of skin testing during pregnancy are poorly defined. Thus, we assumed that she was allergic to local anesthetics and neither ester nor amide type should be considered safe.

The option of parenteral narcotics, including patient-controlled analgesia, for labor was explained. General endotracheal anesthesia was discussed for forceps delivery, cesarean delivery, or episiotomy repair. Preliminary studies by Hurley and Lambert (3) using a 32-gauge microspinal catheter (Microspinal, TFX Medical, Duluth, Ga.), for injection of a local anesthetic for labor analgesia were discussed with the patient. However, as local anesthetics had been ruled

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out, we explored the possibility of using intrathecal opioids for analgesia during labor. Analgesia produced by intraspinal narcotics is, however, often inadequate for the second stage of labor. On the other hand, meperidine, in addition to its mu-receptor agonist property, has direct nerve blocking effects at high concentrations (1,2). We hoped that high-dose subarachnoid meperidine would provide adequate analgesia and anesthesia for labor and delivery. Written informed consent was obtained for a plan to manage labor with continuous spinal meperidine.

At 41 wk gestation, the patient presented after 4 h of stage 1 labor. Obstetrical examination revealed cervical dilation of 3 cm and leaking amniotic fluid. An IV catheter was placed without local anesthetics, and fetal monitoring was instituted. After two more hours of labor, 50 mg of preservative-free meperidine was given via the IV in two divided doses of 25 mg each to provide initial analgesia and to ascertain whether she would have any allergic response to meperidine. This IV meperidine was inadequate to manage the labor pain, and no allergic symptoms occurred.

Continuous finger pulse oximetry and automated blood pressure monitoring were initiated. Sodium bicitrate, 30 mL, was given orally. Intravenous volume loading was completed with 1500 mL of 37°C Ringer's lactate solution. Oxygen (6 L) by face mask was started, and baseline vital signs and the fetal heart rate recorded. With the patient in the lateral position, a 32-gauge continuous spinal catheter was placed in the L3-4 interspace through a 26-gauge spinal needle. The catheter was advanced 2 cm into the subarachnoid space without eliciting a paresthesia. The patient was then placed in the 45° head-up position with left lateral hip displacement. Maternal vital signs were stable, and the fetal heart rate and variability were normal. One-tenth milliliter (5 mg) of meperidine (Demerol Hydrochloride, Winthrop Pharmaceuticals, New York, N.Y.; preservative-free 50 mg/mL, specific gravity of 1.0086 at 20°C, pH 6) was injected through the spinal catheter over 1 min. A reduction in labor pain occurred in 20 min. Two additional doses of 5 mg (0.1 mL) were given, and sensory analgesia to pinprick was present in the T10-L5 dermatomes bilaterally. Leg heaviness also developed in the T10-L5 distribution bilaterally, as well as a 2/4 motor block by Bromage criteria. Maternal vital signs remained stable, and the fetal heart rate and variability remained normal. Complete relief from labor pain was obtained. No sacral anesthesia was demonstrated by pinprick.

For the second stage of labor, sacral anesthesia was obtained by injecting 10 mg meperidine in a 1:1 mixture of meperidine (50 mg/mL) and 10% dextrose, with the patient in the sitting position. It was noted that the amount of meperidine required to produce the same degree of comfort seemed greater than it was earlier in labor when isobaric meperidine was used. A total of 50 mg of meperidine in dextrose was injected over 30 min in three divided doses before the patient reported complete pain relief. She also spontaneously reported that her legs and buttocks were numb. Analgesia to pinprick was noted in the sacral and low lumbar distribution. Motor blockade remained at 2/4 by Bromage criteria.

The initial 50-mg hyperbaric dose gave 1 h of total pain relief. Subsequently the patient required hourly reinjections with 25 mg of hyperbaric meperidine to maintain comfort. She was able to push effectively during the second stage of labor. Additional 25-mg doses of hyperbaric meperidine were given 30 min and again 5 min before actual delivery. The patient had analgesia to pinprick over the perineum and to T-12 distribution before delivery. A vigorous 3.5-kg female infant was delivered spontaneously with 1- and 2-min Apgar scores of 9 and 9, respectively. Forceps were not required. The motor block resolved within 40 min of the last injection of hyperbaric meperidine (before delivery); the sensory block to pinprick lasted about 70 min. Maternal monitoring after delivery included impedance apnea monitoring and finger pulse oximetry for 24 h. No respiratory depression (defined as respiratory rate <10 breaths/min or oxygen saturation of <95% by finger pulse oximetry) was seen. The only side effect noted was mild pruritus of the chest and neck on two occasions; this was managed with a single IV dose of 0.1 mg naloxone. The patient did not develop a postdural puncture headache. She experienced no pain with the episiotomy, delivery, or repair of the episiotomy and third-degree tear, which took 25 min. In addition, the patient moved herself, with slight assistance, from the delivery table in the operating room.

The total meperidine dose was 222 mg over 9 h. The maternal venous plasma meperidine level was 0.4 mg/L (therapeutic range for our laboratory is 0.2–0.5 mg/L). Meperidine readily crosses the placenta (4). Yet, despite repeated maternal doses, this infant had no signs of respiratory or cardiovascular depression after delivery. The neonatal meperidine level in umbilical arterial plasma was 0.2 mg/L. Routine postnatal and nursery care was given. A neurologic examination 12 h after delivery was normal. Scanlon neurobehavioral testing at 2 days after delivery was also normal.

Discussion

Allergic reactions to amide local anesthetic agents are rare (5). Allergic reactions to ester local anesthetics, more frequently reported, are probably due to sensitivity to *p*-aminobenzoic acid and its metabolites. In the present case it was not possible to identify positively the offending agent. After consultation with an allergist, it was decided that the risk to the mother and fetus associated with skin testing outweighed the benefit of any possible data to be obtained. In addition, the advisability of such testing during pregnancy is undefined. We believed it prudent to avoid all local anesthetics in this patient until the agent to which she was allergic could be determined. Future skin testing in an appropriate medical facility was planned for 6 mo after delivery.

The obstetrician considered the likelihood of a long labor and difficult delivery to be significant based on fetal size and pelvic measures in this overdue primigravid patient. The patient, an intelligent and articulate professional woman and excellent informant, described herself as having a low pain threshold, and she consulted the obstetric anesthesia service about her anesthetic options.

Conservative anesthetic management could have included parenteral narcotics (including patient-controlled analgesia) and sedation for the first stage of labor. General endotracheal anesthesia with rapid sequence induction and cricoid pressure could be used for episiotomy, forceps delivery, vaginal/rectal repair, and cesarean delivery. Epidural narcotics by themselves are generally inadequate for the management of the pain of labor and delivery (6). In addition, the large-bore needle required to place a standard epidural catheter was not enthusiastically received by the patient.

Although early reports on the use of intrathecal morphine for labor were enthusiastic (6), it soon became clear that the technique, while useful in early labor, did not provide adequate pain relief for the second stage (7). Intrathecal morphine is also associated with a significant incidence of side effects, including somnolence, severe pruritus, nausea, and vomiting. Leighton et al. reported some success with a combination of intrathecal morphine and fentanyl using a single-dose technique (8). However, we were intrigued with the reports of the efficacy of high-dose meperidine in the subarachnoid space (1,2,9). Meperidine apparently acts at spinal mu-receptors as do morphine, fentanyl, and hydromorphone. However, it also has some local anesthetic activity and is capable of producing varying degrees of motor, sensory, and sympathetic block (10). This property would seem to make possible the use of intrathecal meperidine alone in labor, because in high doses meperidine's nerve blocking effect could potentially provide the additional analgesia needed for the second stage of labor and anesthesia for episiotomy and possibly cesarean delivery.

The use of high-dose spinal meperidine as the sole agent for spinal anesthesia in urologic patients has been reported. Acalovschi et al. (11), for example, used 5% preservative-free meperidine, 0.5 mg/kg, as the sole agent to provide spinal anesthesia in 111 patients for perineal operations. Patel reported that meperidine compared favorably with intrathecal local anesthetic for endoscopic urologic procedures (12). Single injection high-dose intrathecal meperidine has been reported to provide adequate anesthesia for cesarean delivery (13). We believe that its use in our obstetric patient was appropriate when combined with a continuous spinal technique, as the level of analgesia or anesthesia could be titrated in a controllable fashion. The risks, benefits, and experimental status of this option were reviewed with this patient (before labor), and written informed consent was obtained.

As commercially supplied, 5% meperidine is isobaric or slightly hypobaric at room temperature, with a specific gravity of 1.0086. Serial intrathecal injections in our patient provided sensory analgesia, anesthesia, and then motor block in the T10-L5 distribution. Sacral analgesia was then obtained with hyperbaric meperidine (5% meperidine mixed 1:1 with 10% dextrose). Careful trial and error titration demonstrated that a dose of 25 mg isobaric meperidine provided excellent analgesia for approximately 60 min. No significant reduction in maternal blood pressure was seen.

Certainly, the therapeutic level (0.4 mg/L) of meperidine present in the maternal plasma at delivery may have contributed to the analgesia experienced by the patient. However, the analgesia from the intrathecal meperidine was complete and much superior to the IV meperidine administered before instituting the intrathecal injections. The neonatal plasma level in the umbilical artery, 0.2 mg/L, was somewhat higher than that measured by Kuhnert et al. (14): they reported a mean umbilical artery meperidine level of 0.064 mg/L after administration of 50 mg IV meperidine during labor. However, the infant in this case exhibited no signs of respiratory or cardiovascular depression after delivery.

The combination of continuous spinal microcatheter technique and high-dose spinal meperidine can provide flexible and controllable analgesia and anesthesia for labor and delivery.

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A Technique for Obtaining Successful Sacral Spread With Continuous Lumbar Epidural Anesthesia

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Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—sacral spread.

Techniques for obtaining sacral spread of the injected local anesthetic solution are necessary in many instances for assuring successful lumbar epidural anesthesia. Normally, the level of skin analgesia during continuous lumbar epidural anesthesia extends more cephalad than caudad from the site of injection (1), with analgesia taking longer to develop in the first sacral dermatome than in the second and third sacral dermatomes because of the differences in nerve root size (2,3). In this study we compared the extent of loss of cold sensation in the sacral area when two different methods of injecting local anesthetics into the epidural space were used: in one the injection was made through both the epidural needle with bevel pointed caudally and through the catheter; in the other the injection was made through the epidural catheter only.

Methods

Forty gynecologic patients without neurological disease, hypertension, diabetes mellitus, large intraabdominal mass, or pregnancy were studied. All patients were informed about the nature of the study, and consent was obtained. They were premedicated with atropine (0.25–0.5 mg) and hydroxyzine (25–50 mg) 45 min before the procedure. A 17-gauge Tuohy needle was inserted into the epidural space at the L3-4 interspace using a midline approach and a loss of resistance technique with the bevel pointed in a cephalad direction.

We used two methods for injection of a total volume of 15 mL of 2% mepivacaine without epinephrine. In group A (20 cases), the epidural catheter was advanced 5 cm cephalad into the epidural space and fixed in position; after careful aspiration, a test dose of 3 mL of 2% mepivacaine was injected. After turning the patient to the supine position and assuring that the test dose had not been injected intravascularly or into the subarachnoid space, the remaining 12 mL of 2% mepivacaine was injected through the catheter 3–5 min after the test injection. In group B (20 cases), the bevel of the epidural needle was pointed in a caudad direction, and, after careful aspiration, 5 mL of 2% mepivacaine was injected within a few seconds, after which the bevel was pointed in the cephalad direction and an epidural catheter introduced, with the remaining 10 mL of 2% mepivacaine being injected through the catheter 3–5 min after the caudad injection.

The cutaneous extent of loss of cold sensation was determined using a swab of cotton wool soaked with absolute alcohol 15 and 25 min after the test injection, with special attention being paid to cold sensation in the first sacral segment (2,3). The dermatomal chart described by Cousins and Bromage was used for the mapping (1). The loss of cold sensation was used for the determination of the spread of epidural anesthesia because Wugmeister and Hehre have reported that anesthetic levels to cold and pinprick sensation showed little or no change between 15 and 30 min (4). Moreover, repetitive noxious stimulation to skin to measure the level of analgesia might cause skin damage and discomfort to the patient.

Statistical analysis was performed using the nonpaired *t*-test or Wilcoxon rank-sum test. $P < 0.05$ was considered statistically significant.

Results

There were no cases of failed or unilateral epidural anesthesia. There were no significant differences in

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Table 1. Patient Characteristics

	Group A (n = 20)	Group B (n = 20)	P
Age (yr)	45.6 ± 11.8	44.6 ± 13.5	NS
Height (cm)	153.5 ± 3.5	152.2 ± 4.8	NS
Weight (kg)	51.1 ± 5.7	51.6 ± 7.2	NS

NS, not significant.
Values are mean ± SD.

Table 2. Cephalad and Caudad Levels of Loss of Cold Discrimination in the Two Groups 15 and 25 Min After Epidural Injection

Loss of cold sensation	Group A (n = 20)		Group B (n = 20)	
	15 min	25 min	15 min	25 min
Cephalad level	T-8.5 (T-2 to T-12)	T-5.5 (T-1 to T-12)	T-8 (T-1 to L-1)	T-5.5 (T-1 to T-11)
Caudad level	L-3 (L-1 to S-3)	S-3 (L-2 to S-4)	S-3 (L-1 to S-4)[a]	S-3 (S-3 to S-5)[a]

Values are the medians, with the ranges given in parentheses.
[a] $P < 0.01$. Wilcoxon rank-sum test, compared to group A.

age, height, and weight between the two groups (Table 1).

The cephalad level of the loss of cold sensation 15 min after the injection was T-8.5 (T-2 to T-12) (median [range]) in group A and T-8 (T-1 to L-1) in group B; 25 min after the injection these were T-5.5 (T-1 to T-12) and T-5.5 (T-1 to T-11), respectively. There was no significant difference in the cephalad level between the two groups.

The caudad level of loss of cold sensation 15 min after injection was L-3 (L-1 to S-3) in group A and S-3 (L-1 to S-4) in group B ($P < 0.01$). Twenty-five minutes after injection, these were S-3 (L-2 to S-4) for group A and S-3 (S-3 to S-5) for group B ($P < 0.01$, Table 2).

Twenty-five minutes after the injection, complete blockade in the third sacral dermatome was present in 11 patients (55%) in group A and in 20 patients (100%) in group B. However, the number of patients who had complete blockade of the first sacral dermatome was low in both groups, 2 (10%) and 13 (65%), respectively.

Discussion

Many factors—such as a site of injection, nerve root size, weight, height, age, posture, speed of injection of local anesthetic, volume, concentration, and type of local anesthetic agent—affect the efficacy and spread of epidural blockade (1,5–12). In our study, caudad spread of loss of cold sensation was greater after an initial injection of local anesthetics through an epidural Tuohy needle with its bevel pointed to caudad than it was when the entire injection was made through the epidural catheter. There were no significant differences in other factors that might affect the spread of anesthetic level; therefore, our results can be ascribed to the difference in the method of injection of the local anesthetic solution into the epidural space.

Why was the extent of loss of cold sensation in the sacral area so great with partial caudad injection of mepivacaine through the Tuohy needle? It has been reported that epidural pressure affects spread of anesthetic solutions in epidural space (10,11). The initial caudad injection might create greater epidural pressure and thus greater spread of loss of cold sensation than an injection through a catheter advanced in a cephalad direction alone. Equally likely—or even more likely—the direction in which the bevel of the Tuohy needle was pointing at the time of injection might have been responsible for the increased spread in the sacral area.

It has been reported that rotation of an epidural needle may puncture the dura mater, and thus an epidural needle should not be rotated in the epidural space (13). Although there was no case of dural puncture in our study while rotating the epidural needle from caudad to cephalad, the possibility of dural puncture should be kept in mind.

There are conflicting reports of the sacral spread of analgesia during injection of local anesthetic into the lumbar epidural space. Galindo et al. reported that the failure to block the first sacral segment occurred in 20% of patients (2,3). On the other hand, complete sacral analgesia has been reported by some investigators (9,12). Although there is a difference between testing for cold discrimination and testing for pain (pinprick) when evaluating spread of local anesthetic in the epidural space, our results showed the same incomplete sacral anesthesia as reported by Galindo et al.

We conclude that the initial partial injection of local anesthetic solution through an epidural Tuohy needle with its bevel pointed in the caudad direction before injecting the remainder of the local anesthetic through an epidural catheter directed in a cephalad direction results in greater spread of anesthesia in the sacral area than does the same amount of local anesthetic solution injected into an epidural catheter only.

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Total Spinal Anesthesia After Caudal Anesthesia in an Infant

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Key Words: ANESTHESIA, PEDIATRIC.
ANESTHETIC TECHNIQUES, EPIDURAL—caudal.

Preterm children are at great risk of postanesthesia apnea. This risk decreases with age but is still high up to 60 wk postconceptual age (PCA) (1). The occurrence of apnea has been linked to the use of inhalation and intravenous anesthetics as well as to sedatives and narcotics. For this reason spinal anesthesia has been suggested as the anesthetic technique of choice for surgery below the umbilicus in ex-preterm infants under 60 wk PCA (2–4). Spinal anesthesia in infants can be an easy, safe, and reliable technique that provides adequate intraoperative anesthesia lasting 45–90 min (5) with little or no changes in blood pressure (6) and without affecting respiration postoperatively (7). However, with this anesthesia technique, as with any other technique, life-threatening complications can occur as is demonstrated by the following case report.

Case Report

A male born at 27-wk gestation and weighing 1070 g at birth presented at 46 wk PCA with a right-sided inguinal hernia. The child was to undergo hernia repair before being discharged from the hospital, where he had been since birth because of hyaline membrane disease, a patent ductus arteriosus, and infection. He was extubated at 2.5 mo of age (1 mo before the time of surgery), and oxygen therapy was no longer needed 4 days before the time of surgery. On admission to the surgical ward, at 46 wk PCA, the child weighed 3.5 kg, was normally neurologically developed for his age, and had no findings on examination other than a minor systolic murmur and bronchial dysplasia but with blood gas tensions within normal limits. The spine appeared normal on physical examination and on x-rays obtained during his stay in the pediatric intensive care unit.

No premedication was given, and, after cannulation of a vein for fluid infusion, three unsuccessful attempts at spinal puncture with a 22-gauge, 7-cm-long spinal needle were made. As cerebrospinal fluid (CSF) was never obtained and blood was found on the last attempt, it was decided to do a caudal block. For this the child was placed on his left side, and the sacral hiatus easily palpated. A 24-gauge, 2.5-cm-long butterfly needle was inserted through the skin and subcutaneous tissue, and, after easily penetrating the sacral ligament, the needle was not advanced further. After negative aspiration for blood and CSF, a test dose of 0.5 mL of 1% lidocaine (5 mg) with 1/200,000 epinephrine was given. After a minute of observation without change in heart rate or blood pressure and no evidence of motor block, the remaining volume of local anesthetic solution was slowly injected. The total amounts of lidocaine and bupivacaine given were 4.28 mg/kg and 1.42 mg/kg (1.5 mL 1% lidocaine + 1 mL 0.5% bupivacaine with 1/200,000 epinephrine).

As the child was being placed in the supine position he became ashen with cyanotic mucous membranes. Oxygen saturation (Sao_2), which had been at 90%–95%, decreased rapidly. Heart rate decreased from 160–170 beats/min to less than 50 beats/min. There were no breath sounds or respiratory movements. While being given oxygen by mask and manual external chest compression, he was intubated and given 20 μg/kg atropine, 1 mEq/kg sodium bicarbonate, and 10 mL/kg fluids intravenously. Within less than 1 min heart rate was 150 beats/min, systolic blood pressure, which had been too low to be recorded by the automatic blood pressure cuff, increased to 90 mm Hg with an Sao_2 of 90%–92%. The child was totally paralyzed, unconscious, and with bilateral nonreactive dilated pupils. Surgery was cancelled, and the child was transferred to the pediatric intensive care unit where he was mechanically ventilated with 60% inspired oxygen. Arterial blood gas

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tensions were normal, as were blood pressure, heart rate, urine output, and rectal temperature. The electroencephalogram showed a "slow" wave pattern. One hour and 20 minutes after the caudal block spontaneous motor activity resumed, first with blinking of his eyelids, followed by small movements of his hands, and, finally, normal overall motor function at 1.75 h. At 2 h pupils were centered, symmetrical, of normal size, and reactive to light. The child opened his eyes spontaneously. Five hours after the caudal block the child was extubated, and the next morning normal oral feedings were resumed, at which time neurological examination and electroencephalogram were normal for age.

A blood sample drawn 15 min after the caudal injection of local anesthetics had a lidocaine plasma concentration of 0.96 μg/mL and a bupivacaine plasma concentration of 0.4 μg/mL, both far below the concentrations considered to be toxic for the brain and the myocardium. Follow-up examinations 1 and 4 mo later showed normal neurological development.

Discussion

Two diagnoses come to mind in this case: systemic toxicity due to intravascular injection of local anesthetics and total spinal anesthesia.

Although no blood was aspirated before the injection of the test dose into the caudal canal, and although there was no change in heart rate thereafter, this unfortunately did not rule out intravascular injection. In this small child the 24-gauge butterfly needle that was used did not have a stylet, and tissue trapped in the lumen of the needle as it was moved into the caudal canal may have prevented aspiration of blood while allowing intravascular injection of the solution. Also, an epinephrine-containing test dose does not always produce an increase in heart rate and blood pressure indicating intravascular injection in children (8). Plasma concentrations of local anesthetics found in this patient were too low to cause systemic toxicity but do not indicate what peak levels might have been immediately after injection. The sole blood sample was taken 15 min after injection of the local anesthetic solution. Had the injection been intravascular, 15 min later blood levels of the local anesthetics would have decreased well below peak plasma concentrations.

The most probable diagnosis in this case was total spinal anesthesia after caudal injection of local anesthetics. Supportive of this diagnosis were the sudden, profound, and complete motor block with cessation of respiration, both of which spontaneously disappeared after 1.5 h, bilateral mydriasis, which regressed completely within 2 h, and plasma concentrations of local anesthetics compatible with those usually found 15 min after subarachnoid injection.

Two hypotheses can be brought forward to explain how the total spinal occurred. Although there was no spontaneous flow of CSF out of the needle in the caudal canal and no CSF on aspiration, puncture of the dural sac could have occurred but have been missed. Again, the needle was small and did not have a stylet, and some skin or subcutaneous tissue caught in the lumen of the needle may have prevented aspiration of CSF yet have allowed injection into the subarachnoid space. In a 2-mo old infant the lower extremity of the dural sac can be as low as the S-3 or S-4 level, sometimes less than 1 cm from the sacral hiatus (9). As the needle was not advanced after penetrating the sacral ligament, the lower termination of the dural sac might in this case have been at the sacral hiatus. Although not found in this child on physical examination or x-rays, sacral anomalies are present in 10% of people, and malposition of the dural sac is always possible and can be difficult if not impossible to detect clinically (10). On the other hand, the standard volume of local anesthetic for a 3.5-kg "premie" spinal is 0.6–0.75 mL, and, had the local anesthetic solution been injected intrathecally, the 0.5-mL test dose given would probably have produced a complete motor block of the lower limbs within the minute we allowed for test dose observation.

Another hypothesis is that repeated punctures of the dura mater during the spinal attempts produced holes through which the local anesthetics later leaked from the epidural space into the subarachnoid space. In a small baby the distance from the sacral hiatus to the L4-5 interspace is small, at most 2–3 cm, tissues are fragile, and the pressure with which the local anesthetics are injected comparatively high. A fraction of the total volume of local anesthetic solution injected into the caudal canal (2.5 mL, here), let us say 1.5 mL, if injected under enough pressure to open up the holes in the dura mater, would have been enough to produce a total spinal in a 3.5-kg child. On the other hand, a fraction of the 0.5-mL test dose would have been insufficient to produce a motor block. This could explain why there was no noticeable block after the test dose.

In conclusion, although spinal anesthesia is advocated for ex-preterm infants who are to undergo short lower abdominal surgery because this technique seems to reduce postanesthesia life-threatening apnea that may be associated with general anesthesia (11), this case report shows that spinal and caudal anesthesia in ex-preterm infants have their own potential for complications. One must always keep in mind that termination of the dural sac is nearer the sacral hiatus in infants than in adults, and that sacral and dural sac anomalies exist and can go undetected by simple physical examination and x-ray. When performing a caudal block in an awake infant, great care and sufficient time should be taken not only to detect intravascular injection but also to detect motor blockade before injecting the total dose of local anesthetic. In view of this case, however, we believe that because leakage of local anesthetic from the epidural space into the subarachnoid space may occur through holes in the dura produced during unsuccessful attempts at spinal anesthesia, caudal anesthesia should not be attempted after repeated spinal punctures in ex-preterm infants.

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Letters to the Editor

Venous Embolism During Cesarean Section

Key Words: ANESTHESIA, OBSTETRIC—air embolism. EMBOLISM, AIR—obstetric.

To the Editor:

Karuparthy et al. (1) report findings that confirm the high incidence of precordial Doppler-diagnosed venous "air" embolism during cesarean section. Attempts to increase uterine venous pressure by the head-up position did not affect the incidence of embolization. How can we know that it was air that was embolizing, and not amniotic fluid contents? The latter would account for the absence of benefit from the head-up position.

The precordial Doppler is quite sensitive (but not specific) to inhomogeneities in blood, such as air bubbles, that alter the velocity of sound waves and thus reflect the waves. Would not the contents of the typical amniotic fluid embolus (squamous cells, hair, fat, meconium) similarly reflect sound waves? It seems quite possible to me that minor, subclinical amounts of amniotic contents could be detected, without producing the full-blown, catastrophic clinical picture. Blood samples drawn at random times from the pulmonary arteries of parturients catheterized to help manage severe toxemia have yielded squamous cells and trophoblastic cells (but not mucous threads or fat droplets) in the absence of clinical signs of amniotic fluid embolism (2,3). Have experiments been done in which central venous blood sampled during embolization associated with cesarean section has been examined for amniotic contents in order to exclude the possibility of amniotic fluid, not air, being the source of venous embolization during cesarean section? Another group for comparative precordial Doppler auscultation would be parturients during vaginal delivery.

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In Response:

I thank Dr. Meyer for his comments concerning our paper (1) reporting on the incidence of venous air embolism during cesarean section. His point regarding the ability to differentiate between air and amniotic fluid content using the Doppler technique is well taken.

The precordial Doppler method is indeed a sensitive tool. However, Clark et al. (2) "have demonstrated that squamous cells are almost universally detected in the pulmonary arterial circulation of pregnant patients." In the light of the above, we would have expected to report an almost 100% incidence of venous embolism rather than the 11% actually detected. Others of course have described surprisingly high incidences (3,4). Could this be due to their use of more sensitive Doppler transducer systems allowing detection of particulate matter as well as air?

However, a primate study conducted in our own anesthesia research laboratories (5) and ongoing clinical investigation of patients undergoing coronary artery bypass surgery here suggest that it is possible to differentiate between air and solid particles invading the circulation.

Future research along similar lines in parturients will perhaps provide a definitive answer to Dr. Meyer's thoughtful and clinically pertinent question.

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Emergency Suction in a Parking Lot

Key Words: EQUIPMENT, SUCTION—portable.

To the Editor:

As part of our emergency protocol for mass casualties, triage occurs in the parking lot in front of our emergency room. In the aftermath of the recent earthquake in San Francisco there was the potential for hundreds of patients to present to our facility, many of whom might have required emergency airway management. Most of the equipment needed is portable and can be provided in large quantities, e.g., laryngoscopes, ATF bags, oxygen tanks, and endotracheal tubes. Suction, however, cannot be provided as easily or in large quantity. An option that provides excellent suction and a large capacity is easily made from a 60-mL monoject Toomey syringe with a 15-cm piece of suction tubing fit over its end (Figure 1). Laryngoscopy can be done with the left hand and suction with the right hand to clear any secretions that might obscure the view of the cords. Fortunately, the number of patients who presented to our hospital and required emergency airway management was small. However, I have used this device in the operating room on numerous occasions and believe that it would be useful in the mass casualty situation.

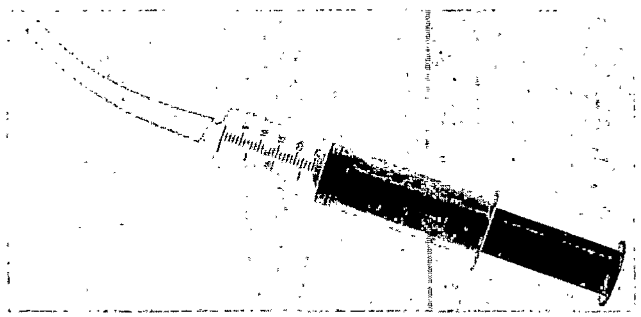

Figure 1. Sixty-milliliter syringe with suction tubing attached for emergency portable suction.

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Somatostatin Neurotoxicity in Animals

Key Words: HORMONES, SOMATOSTATIN.
TOXICITY, SOMATOSTATIN.

To the Editor:

The recently published letter to the editor from Dr. Chrubasik (1) and the response from Dr. Yaksh (2) deserve, we believe, amplification from investigators working in this field.

In 1983, before clinical use of epidural somatostatin, animal experiments were carried out to evaluate whether epidural somatostatin causes neurotoxic effects. The investigation was undertaken with the permission of the Commission of Animal Experiments of Baden-Würtemberg, was carried out in the Department of Experimental Medicine of the University of Freiburg, and was supervised by two veterinarians. The spinal cord, dura, and two spinal ganglia were removed from the area where the epidural catheter used for injection of somatostatin had been placed. These sections were fixed in formalin for 2 wk and then embedded in paraffin and stained with hematoxylin-eosin and Kluver-Barrera. The sections from 12 dogs after epidural somatostatin exposure (6 mg/day over 672 h in 10 dogs, 10 mg/h over 5 h in one dog and over 7 h in one dog), as well as sections from one dog after 10 mg/h over 3-h exposure to intrathecal somatostatin, and four controls (epidural saline over 672 h in three dogs, over 7 h in one dog) were examined by pathologists without prior knowledge of the identity of the histologic specimen for signs of neurologic damage, inflammatory response, or demyelination. The results after decoding revealed signs of various degrees of acute inflammation and hematoma in various stages of organization (epidural, subdural, and subarachnoid) attributed to the prolonged epidural catheter placement. In one instance suppurative encephalitis was also noted. Nonspecific damage was less pronounced in the controls. No other pathological changes whatsoever were found in the brain, spinal cord, ganglion, or nerve. There was agreement between us that epidural somatostatin in the dosage used had no neuropathological effect on the canine spinal cord.

It seems obvious that differences in dosages and concentrations as much as 200- and 4–10-fold, respectively (3,4), as well as differences in the route of administration (epidural or intrathecal—only small amounts of epidural somatostatin reach the intrathecal space [5]), might account for reported differences in the histologic effects of somatostatin on the spinal cord. Although clinical investigations with epidural somatostatin have not revealed any adverse effects (6–9), there is no doubt that further histologic investigations are necessary to evaluate the epidural somatostatin safety range.

If intrathecal somatostatin—administered to a very limited number of terminal cancer patients (6,10)—should be further employed, of course the intrathecal somatostatin safety range has to be determined also.

As proposed elsewhere (1), a general rule should be established concerning the animal model and the factor by which the clinically effective per body weight dose of a substance and its concentration in solution need to be multiplied in order for them to be employed epidurally and intrathecally without having deleterious side effects.

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Corrigendum for Bronchial Diameters

Key Words: ANESTHETIC TECHNIQUES, ENDOBRONCHIAL—cuff pressures.

To the Editor:

We wish to correct two of our own errors contained in a paper we recently published in this journal (1). In this paper we stated that our measurements of double-lumen-tube bronchial-cuff pressure and volume at occlusion were obtained with the bronchial lumen contained in a 12-mm glass cylinder. We cited a standard reference work (2) in stating that 12 mm is the diameter of the average male's left main-bronchus. We now report that

(a) The diameter of our glass cylinder was NOT 12 mm. By remeasuring occlusion volumes in different size cylinders we now estimate that the actual cylinder diameter measured between 14 and 15 mm.

(b) Primary literature concerning measurement of bronchial size in cadavers (3) suggests that the figure of 12 mm quoted from the textbook is in any event *not correct.* This paper reports that the measured diameter of the male left main-bronchus is 15 ± 1.9 mm.

The data in our paper are correct and need no alteration. Only the conditions under which the data were acquired are described incorrectly. It appears that we fortuitously used a cylinder whose diameter corresponded closely to the diameter of the average male's left main-bronchus. We apologize for the error and wish to set the record straight both about our study and about the appropriate value for the diameter of the typical left main-bronchus.

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A Three-Way Stopcock as a Universal Anesthetic Adapter for Metered Dose Inhalers

Key Words: EQUIPMENT, INHALER—metered dose.

To the Editor:

There have recently been two reports of adapters allowing the use of metered dose inhalers (MDI) in anesthetic breathing circuits (1,2). At our institution, we have solved this problem in a different way.

We use a Sorenson Research three-way stopcock. This is commercially produced and routinely stocked in all our operating rooms. It is supplied with two caps, one of which

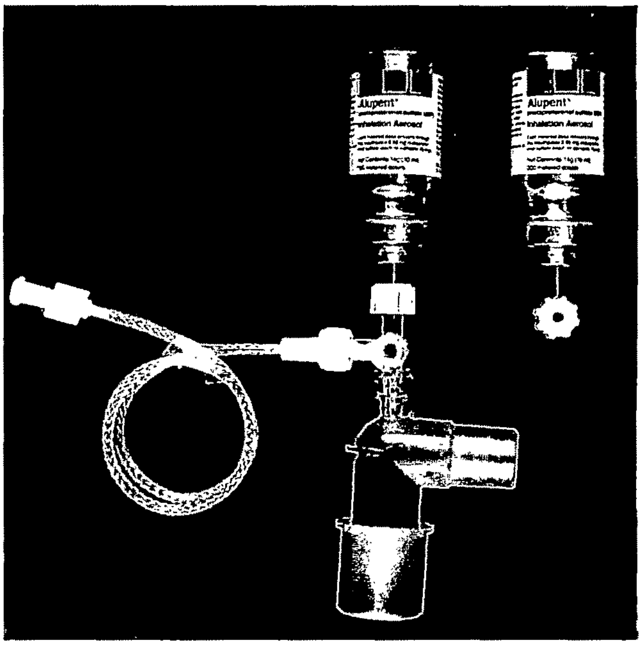

Figure 1. **Left**, the MDI and stopcock in position, connected to the angle piece of the breathing circuit. **Right**, the nozzle of the MDI fits tightly into the hole of the vented cap.

is vented. The stopcock fits onto the Luer-lok port on the angle piece of the breathing circuit for carbon dioxide (CO_2) sampling. The vented cap fits onto the end port of the stopcock; the nozzle of any MDI will fit snugly into the hole in the cap. The CO_2 sampling line may then be fitted onto the side port of the stopcock (Figure 1).

This system has distinct advantages. First, CO_2 monitoring may be continued between administrations of bronchodilator, maintaining a closed system. Second, the MDI will remain in place for repeated use. Third, the MDI can be operated single-handedly, allowing manual ventilation to be performed simultaneously. If the anesthesiologist is concerned about contamination of the CO_2 monitor, the vented cap will connect directly to the CO_2 sampling port.

We have used both methods and have found them to be simple to use with satisfactory results. The equipment needed is readily available without modification when bronchospasm requires prompt therapy.

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Invasive Monitoring of Cardiac Surgical Patients

Key Words: ANESTHESIA, CARDIOVASCULAR—monitoring. MONITORING, COSTS.

To the Editor:

We read with interest the recent article by Pearson et al. (1) with regard to the effect of choice of the invasive monitoring on cost, morbidity, and mortality in cardiac surgery. The authors concluded that the use of central venous pressure (CVP) monitoring in lieu of or without the addition of pulmonary artery (PA) pressure monitoring may be justified in some cardiac surgical patients. Also, they concluded that the use of PA catheters added additional cost and no benefit in outcome, particularly when fiberoptic PA catheters for monitoring mixed venous oxygen saturation ($S\bar{v}O_2$) were used.

Because each monitoring device provides information regarding a hemodynamic component that the physician needs to evaluate, it is important to identify patients at high risk for the development of hemodynamic and oxygen transport imbalances in whom this information is necessary. Patients who have had cardiac surgery represent, by definition, the "ideal" group of critically ill patients with regard to potential physiologic instability. This is probably the reason why 65% of the patients assigned initially to group 1 (CVP) in the study of Pearson et al. (1) were reassigned.

Continuous PA-mixed venous oximetry may be used as "on-line assurance" that oxygen transport balance is maintained. $S\bar{v}O_2$ values of less than 40% usually reflect inadequate hemodynamic function and may be the only sign of impending hypotension, vasoconstriction, arrhythmias, respiratory distress, and/or cardiac arrest. Usually, hemodynamic changes that are not associated with derangements in $S\bar{v}O_2$ are not significant, provided that perfusion pressure is adequate.

Although we are aware of claims that PA catheters are overused for elective cardiac surgery, we believe that their underuse may represent a potentially dangerous situation. Central venous pressure monitoring alone serves as a basis for evaluation of right ventricular function. The right ventricle may remain competent with no change in the filling pressure, despite the existence of left ventricular failure. A normal CVP may be measured in vasodilated hypervolemic patients and vasoconstricted hypovolemic patients, as well as in euvolemic patients with normal vascular tone. Also there is low correlation between CVP and pulmonary capillary wedge pressure (2). On the other hand, changes in pulmonary capillary wedge pressure parallel changes in left ventricular compliance as seen in myocardial ischemia. Also, relief of ischemia by preload and/or afterload reduction will be observed on pulmonary capillary wedge pressure tracing. The addition of $S\bar{v}O_2$ monitoring increases the ability to assess global tissue oxygenation. We think that the correct use of the fiberoptic PA catheter provides hemodynamic data that may have an important impact on early diagnostic and therapeutic decisions. These advantages may offset the cost of the monitoring device. Mistrust in normal $S\bar{v}O_2$ values results in an increased number of unnecessary laboratory measurements and significant costs to the hospital and/or patient. We found unjustifiable the amount of cardiac output and blood gas determinations in groups II–V in the paper by Pearson et al. (1) for the short lengths of stay their patients had in the postoperative intensive care unit.

In view of the fact that every patient in the study of Pearson et al. was monitored with a left atrial pressure catheter, we believe the authors' summary is misleading. Central venous pressure monitoring was justified in their low-risk patients only when combined with left atrial pressure monitoring, and their additional monitoring of $S\bar{v}O_2$ produced no discernible outcome differences again only when compared with the use of CVP and left atrial pressure measurement. The conclusion of this article does not reflect the actual patient monitoring used in the study.

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2. Mangano DT. Monitoring pulmonary arterial pressure in coronary artery disease. Anesthesiology 1980;53:364–70.

In Response:

Thank you for allowing us the opportunity to reply to the letter from Drs. Cernaianu, Moore, and Posner.

We are in agreement with their claims that it is important to identify high risk patients. We also agree that patients undergoing cardiac surgery may become physiologically unstable. As mentioned in the discussion, "decisions to reassign (patients) were based on severity of cardiac disease and followed published recommendations" (1).

Cernaianu and associates claim that "mixed venous oximetry may be used as 'on-line' assurance that oxygen transport balance is maintained." It may be used for such, but not reliably, as is discussed below. They then assert that an $S\bar{v}o_2$ of less than 40% reflects a multitude of problems. We agree that $S\bar{v}o_2$ values of less than 40% are significant, but we must point out that normal $S\bar{v}o_2$ values are greater than or equal to 60% (2). Perhaps this was just a typographical error, and they had mixed venous Po_2 values of 40 torr in mind! In our study we found no patient with low $S\bar{v}o_2$ as the only sign of impending distress. Boutrous and Lee found that "at no time would the $S\bar{v}o_2$ have served as the sole predictive signal for subsequent deterioration of the patient's status" (3). Additionally, in another prospective evaluation of $S\bar{v}o_2$ monitoring in critically ill patients, Jastremski et al. found that "the majority of clinically significant (hemodynamic) events . . . were not associated with any change in $S\bar{v}o_2$. In critically ill patients, clinically important events occur without any change in $S\bar{v}o_2$, and $S\bar{v}o_2$ changes >10% lasting 5 minutes often have no importance" (4). Our objective data also revealed no incident where $S\bar{v}o_2$ provided earlier warning of problems developing without hemodynamic changes. We would be interested in any data that Dr. Cernaianu and associates could produce to support their prejudices about the utility of $S\bar{v}o_2$ monitoring.

Our paper is criticized on the basis that the CVP may be misleading at times. We agree that there are times where CVP monitors will not be reflective of left ventricular filling pressure changes. We remind Dr. Cernaianu that the PA catheter may also mislead the unsuspecting clinician (5). We were surprised to see that Dr. Cernaianu and colleagues chose to refer to Dr. Mangano's 1980 paper to support their claim that the CVP did not correlate with the pulmonary capillary wedge pressure (PCWP). Mangano stated, "The CVP and PCWP correlated well (r = 0.89) during all measurement periods for patients who had ejection fractions greater than 0.50 . . . normality (abnormality) of the CVP was predictive of normality (abnormality) of the PCWP for more than 96 percent of the 450 data points" (6). Our patients in group I confirmed Mangano's observation.

Cernaianu et al. restated our hypothesis, i.e., does $S\bar{v}o_2$ monitoring reduce morbidity, mortality, and costs below that incurred with the use of conventional PA monitoring? Based on our data, we rejected this hypothesis. Cernaianu implied that we did not believe the $S\bar{v}o_2$ values obtained. As stated in the discussion, this study was done after extensive in-service education, and after 9 mo of clinical experience with $S\bar{v}o_2$ monitoring. Additionally, there was no decrease in monitoring costs associated with the $S\bar{v}o_2$ monitoring over the length of the study. Because of these factors, we doubt that "mistrust" in $S\bar{v}o_2$ values increased costs. The authors also claim, "We found unjustifiable the amount [*sic*] of cardiac output and blood gas determinations." As they admitted earlier in their letter that cardiac surgery patients are critically ill, we are surprised they think that two (group II–IV) or three (group IV) determinations of cardiac output and associated derived parameters in the postoperative period are unjustified. We believe that six (groups II, III, V) or seven (group IV) measurements of arterial blood-gas tensions were reasonable. These measurements were made not only to assess oxygenation, but also to measure pH and $Paco_2$, and were needed to guide weaning from mechanical ventilation. The study was performed before availability of pulse oximetry in our surgical intensive care unit. Fewer arterial blood gas determinations are necessary today, but certainly not because of $S\bar{v}o_2$ monitoring.

Finally, the authors claim we misled the readership, and they disagree with our summary, stating that our conclusion did not reflect the actual patient monitoring used in the study. Perhaps they did not read our final paragraph carefully. We stated, "Patients with good cardiac function could safely undergo cardiac surgery with monitoring of only CVP and left atrial pressure [underline added] at considerably reduced cost." We are mystified by their contention that "$S\bar{v}o_2$ produced no discernible outcome differences again only when compared with the use of CVP and left atrial pressure measurement." We actually concluded, "Neither cost, mortality, nor morbidity were reduced in patients requiring PA catheters for cardiac surgery when $S\bar{v}o_2$ monitoring capability was added. Indeed, we found costs associated with $S\bar{v}o_2$ monitoring catheters to be considerably higher." Clearly, our conclusions *did* reflect the monitoring used in our study.

Unfortunately, it appears that Cernaianu et al. read our paper neither carefully nor objectively. Their critical remarks appear to be based on subjective impressions and unfounded beliefs. We did not confirm the bias in favor of $S\bar{v}o_2$ of Dr. Cernaianu and associates. Their criticism of our paper is free of objective data and does not cause us to alter our conclusion.

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Benzyl Alcohol Administration in Neonates

Key Words: TOXICITY, BENZYL ALCOHOL. ANESTHESIA, PEDIATRIC—benzyl alcohol toxicity.

To the Editor:

The important informative letter from Reynolds and Wilton (1) on the potential toxicity of benzyl alcohol in premature infants is (a) incomplete in its listing of drugs that contain

Table 1. List of Parenteral Medications Frequently Used by Anesthesiologists for Which at Least One Formulation Contains Benzyl Alcohol

Pharmacologic action	Generic name	BA-free formulations	Formulations with BA	BA content (mg/mL medication)	Alternatives without BA
Anticholinergic, antisialagogue	Atropine sulfate	Abbott LyphoMed	Astra Elkins	15	
	Glycopyrrolate	—	American Regent LyphoMed Quad Schein Robins	9	
Anticholinesterase	Physostigmine	—	Forest Quad	20	Neostigmine Edrophonium
	Pyridostigmine	ICN	Organon	10	
Anticoagulants	Heparin[a]	LyphoMed Squibb Abbott Winthrop	Organon Wyeth Upjohn Elkins	10	
Anxiolytics	Diazepam	—	Legere Roche Hauck	15	
	Midazolam	—	Roche	10	
Crystalloid solutions	Bacteriostatic saline, water	Abbott[b] Baxter Kendall Elkins	Elkins[b]	9	Preservative-free saline, water
Muscle relaxants					
Short-acting	Succinylcholine	Squibb Abbott Burroughs	Organon	10	
Intermediate-acting	Atracurium	Ampules, 5-mL vial	10-mL multidose vial	9	Vecuronium when dissolved in BA-free solution
Long-acting	Pancuronium	—	Astra Elkins Quad Organon	10	Metocurine Gallamine
	Tubocurarine	Lilly	Abbott Squibb	9	
Respiratory stimulant	Doxapram	—	Robins	9	Naloxone—if narcotic being antagonized
Miscellaneous	Metoclopramide	Quad LyphoMed SoloPak Robins	Robins	9	

BA, benzyl alcohol.

[a] Preparations contain from 1,000 to 10,000 U/mL depending on manufacturer.

[b] Other nonproprietary preparations may be available.

benzyl alcohol and (b) misleading because competing manufacturers' preparations of the same drug do not necessarily contain the same preservatives. For example, two anticholinesterase drugs that can contain benzyl alcohol were not cited, and although Reynolds and Wilton list the one brand of succinylcholine that contains benzyl alcohol, there are three other preparations that do not. Furthermore, they discuss the association of multiple-dose vials with benzyl alcohol, yet "single-dose" 2-mL vials of pancuronium (Astra) also contain benzyl alcohol. Although most reported neonatal complications associated with benzyl alcohol administration involved large volumes of flush solutions containing this preservative, there may not be a direct relationship between the cumulative dose of benzyl alcohol and the incidence of clinical toxicity (2). Indeed, because pathways for the metabolism of benzyl alcohol in the premature infant are poorly developed, exposure to any quantity of this substance is potentially toxic (3).

Our Table 1 comprehensively documents the complex situation as to which formulations contain benzyl alcohol and also those benzyl alcohol-free pharmacologic alternatives that do exist (4,5). Several drug preparations (e.g., doxapram and Robins' glycopyrrolate) display the warning "not for use in newborns" on the label. We urge that all benzyl alcohol-containing drug formulations display this warning. Additionally, as formulations may change with time, their composition should be checked routinely for the presence of chemicals accompanying the intended drug (6).

Available drug formulations may preclude the avoidance of benzyl alcohol administration to the neonate. The American Academy of Pediatrics has emphasized that the presence of benzyl alcohol as a preservative should not prohibit use of medications indicated for treatment of an infant (7). However, anesthesiologists should be aware that the American Academy of Pediatrics (7), Centers for Disease Control (8), and the Food and Drug Administration (9) all recommend that the use of products containing this agent should be avoided in neonates whenever possible. Likewise, it seems prudent to apply these same precautions to pregnant patients within whom the benzyl alcohol molecule, given its small size, presumably crosses the placental barrier into immature fetal tissues as readily as it crosses the blood-brain barrier (10).

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PEEP Valve Barotrauma

Key Words: EQUIPMENT, VALVES—PEEP. LUNG, BAROTRAUMA—PEEP.

To the Editor:

Pneumothoraces occurring during anesthesia due to a variety of equipment related problems have been well reported (1–3). We describe a case in which a malfunctioning PEEP valve resulted in a life-threatening tension pneumothorax during anesthesia.

A 66-yr-old, 60-kg man with a right lung mass was to undergo general anesthesia for a right thoracotomy. Before the induction of anesthesia the anesthesia machine, an Ohio Excel, was tested per manufacturer's recommendations and found to be properly functional, including function of the inspiratory and expiratory valves. After induction of anesthesia, the trachea was intubated, but ventilation of the lungs was difficult and pressure in the anesthesia circuit was high (50–60 cm H_2O). The endotracheal tube was replaced, but attempts at ventilation again resulted in increasing circuit pressures without chest wall excursion and rapid hemodynamic deterioration leading to cardiac arrest. External chest compressions were begun and epinephrine was administered. A blood pressure of 80/50 mm Hg was obtained and the electrocardiogram monitor showed a sinus tachycardia of 110 beats/min. The continued increase in anesthesia circuit pressures led to the recognition of an obstructed circuit. The anesthesia machine was disconnected from the endotracheal tube, and ventilation of the patient utilizing a self-inflating bag with 100% oxygen was started. Compression of the ventilating bag was difficult, and breath sounds were diminished over the right chest. A diagnosis of tension pneumothorax was made. Ventilation improved markedly, and blood pressure promptly rose to 160/90 mm Hg after placement of a right

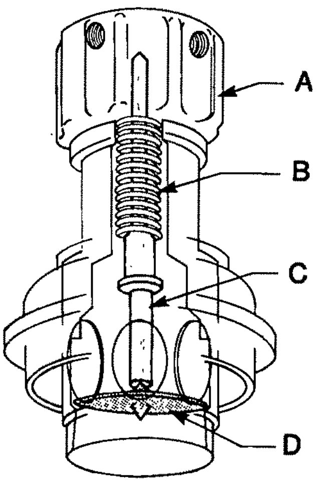

Figure 1. Ohmeda GMS PEEP valve. *A*, control knob; *B*, tension pin spring; *C*, tension pin; *D*, expiratory valve disk.

thoracostomy tube. A replacement anesthesia machine was connected to the patient, and the remainder of the patient's intraoperative and postoperative course was entirely uneventful with the patient suffering no permanent sequelae from the episode. The rapid deterioration of this patient immediately after the development of high breathing circuit pressures along with his rapid improvement after thoracostomy tube placement constitute strong clinical evidence of a tension pneumothorax.

The anesthesia machine initially used was inspected immediately after the incident and the origin of the obstruction was found to be at the PEEP valve. This valve (Ohmeda GMS PEEP Valve stock No. 0207-8223-800) is installed in the dome above the expiratory valve disk. When functioning properly, the valve produces PEEP (2–20 cm H_2O) by a spring-loaded tension pin that presses on the expiratory valve disk (Figure 1). The level of PEEP delivered is controlled by a threaded PEEP valve control knob at the top of the assembly that compresses the spring loading the tension pin. In our valve, this spring and tension pin had become corroded, allowing the rod to bind. During a previous anesthetic, difficulty delivering PEEP with this anesthesia machine and valve was experienced by another anesthesia provider; however, this information was not conveyed to us before this case. We postulate that the tension rod initially was sticking in the "up" position, hence the inability of the valve to deliver PEEP and the lack of interference with function of the circuit during the preoperative checkout. After the induction of anesthesia in our patient, the tension pin evidently shifted its position to exert an uncontrolled force on the expiratory check disk. Because fresh gas inflow continued, high anesthesia circuit pressures developed, causing the difficulty with ventilation and subsequent barotrauma.

Neither the Ohmeda operation manuals for the Excel machine and GMS PEEP valve nor the FDA checkout recommendations for anesthesia machines give specific guidance for preoperative assessment of PEEP valve function (4). As this case illustrates, without a preanesthetic PEEP valve test a malfunctioning valve may be missed by customary machine checkout protocols.

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What Is the Meaning of the Expired CO_2 Waveform?

Key Words: VENTILATION, VENTILATION: PERFUSION RATIO. CARBON DIOXIDE, EXPIRED—waveform.

To the Editor:

Gilbert and Benumof say in their clinical report (1) that the carbon dioxide (CO_2) elimination waveform is an accepted expression of the relationship between ventilation and perfusion (V/Q). I do not believe this to be the case.

To provide support for their contention that "the continuum of V/Q ratios . . . creates a positive slope (upward to the right) to the alveolar plateau part (phase 3) of the CO_2 elimination waveform" the authors cite three pages from Nunn (2).

There is no discussion of V/Q in relation to expired CO_2 in the Nunn reference. Nunn describes (see his Figure 7.3D) the model of two lung units with different time constants—a time constant is the product of resistance and compliance of a given unit—to explain the positive slope of the curve of nitrogen expired after the inhalation of a single breath of 100% oxygen (O_2). Nitrogen, as an inert gas, is classically used to measure distribution of ventilation (3) because it is not involved in gas exchange as are O_2 and CO_2 (4). The reference cited (2), therefore, does not support the notion considered by Gilbert and Benumof (1).

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In Response:

Dr. Cruz seems to be focused on a literal accounting of Dr. Nunn's words rather than on the *meaning* of the words. Dr. Nunn states that "slow units are slow both to fill and to empty, and thus are *hypoventilated* for their volume" (1). Given a reasonably uniform distribution of perfusion (as is the case in most supine anesthetized patients), a slow unit must be relatively hypercapnic (compared to a fast unit). Because "gas from the slower unit forms a proportionately greater part of the end-expiratory gas" (1), a lung that has a significant maldistribution of fast and slow units, that empty sequentially, must have a significant positive slope (upward to the right) to the alveolar plateau part (phase 3) of its carbon dioxide elimination waveform. Thus, given a relatively uniform distribution of perfusion, slow hypercapnic units, and sequential emptying (as is the case with "maldistribution due to the commoner forms of lung disease" [1]), the carbon dioxide elimination waveform does reflect ventilation/perfusion relationships in many patients (2). In fact, taking this notion one step further, absolute airway resistance and increases in airway resistance (which increase the maldistribution of fast and slow units) correlate very well with the slope, and increases in the slope, respectively, in the alveolar plateau of the carbon dioxide elimination waveform of supine anesthetized patients (3).

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Regional Anesthesia for Repair of Zenker's Diverticulum

Key Words: GASTROINTESTINAL TRACT, ESOPHAGUS—Zenker's diverticulum.

To the Editor:

The recent article by Thiagarajah et al. (1) concerning the problems associated with general anesthesia for repair of Zenker's diverticulum was appropriate in regards to this approach to the problem. There is, however, another anesthetic approach to this operation that obviates many of the issues raised by Dr. Thiagarajah and his colleagues.

In 1961 Dr. Clement Hiebert of our institution began repairing Zenker's diverticulum using regional anesthesia. This anesthetic technique consisted of blocks of the deep and superficial cervical plexus as described by Murphy (2). In 1976 Dr. Hiebert published his experience (3). He has taught this technique at surgical symposia all over the world. As of September 1989, 58 patients have undergone surgery for repair of their Zenker's diverticulum, all with regional anesthesia and without failure of the regional technique.

We use a light premedication, usually administered in the operating room just before the placement of the blocks. Little or no sedation is given during the procedure with the objective of having the patient awake and alert, a factor that is important for a successful operation. Having the patient awake allows him or her to swallow on command, enabling the surgeon to view the pathology "in action." The patient is fed small spoonfuls of Jello after the repair with the incision still open so that the surgeon can insure the adequacy of the correction under direct vision. These patients do not require a recovery room stay, and they may get up, eat, and drink immediately upon completion of the surgery. Total operative time is approximately 1 h.

I believe that there are obvious advantages to this approach in the geriatric population. We have had no anesthetic complications in the series of 58 patients.

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Book Reviews

Atlas of Color Doppler Echocardiography

N. C. Nanda. Philadelphia: Lea & Febiger, 1989, 544 pp, $135.00.

Textbook of Color Doppler Echocardiography

N. C. Nanda. Philadelphia: Lea & Febiger, 1989, 359 pp, $110.00. (Combined price, $220.00.)

Intraoperative echocardiography is the most recent addition to the armamentarium of the anesthesiologist caring for patients with cardiovascular disease. Nanda's *Textbook and Atlas of Color Doppler Echocardiography* provides a comprehensive discussion of the basic concepts and clinical application of Doppler, both of spectral analysis and of color flow. The chapter entitled "Echocardiographic Examination Technique: A New Practical Approach" is a well-written and succinct discussion of two-dimensional echocardiography. The text is easy to read and to understand. The editor and chapter authors are recognized leaders in echocardiography. Although written for echocardiographers, extensive training in cardiology is not required. The text and atlas would serve nicely as a reference during a 3-mo rotation in a noninvasive echocardiography service.

The text comes in two volumes, the first in textbook style and the second in atlas format. Each volume is sold separately, and there is also a set of slides available to accompany these two volumes. The first volume is useful for the anesthesiologist interested in intraoperative Doppler because it provides a complete and full informative text. M-mode and two-dimensional echocardiography are not emphasized, because this is not the intent of the book. The text also presents the new areas of technologic developments in the field. The list of references directs the reader to complementary information but is not exhaustive, as it has few references from the anesthesia literature.

The atlas in general is an impressive collection of color plates of remarkable quality. There usually is a great deal of loss of resolution in taking images from video tape to single-frame photos. However, in this edition Dr. Nanda and his group of sonographers have set a new standard of premier quality images.

From an anesthesiologist's perspective the two-volume set is a useful resource. Its major drawbacks include (a) a relatively small section on intraoperative color Doppler with few color plates of transesophageal and epicardial case studies, and (b) the absence of comprehensive chapters on imaging techniques (i.e., M-mode and two-dimensional echocardiography). The complete set of two volumes and the slides is expensive, but they may serve as a valuable resource for those individuals who are interested in the current state of affairs in echocardiography.

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Anaesthesia and Malignant Disease

J. Filshie and D. S. Robbie, eds. Dobbs Ferry, N.Y.: Sheridan House, 1989, 303 pp, $55.00.

In the United States, the population over 65 yr old is expected to increase to 66 million by the middle of the next century. As malignant disease is mainly a disease of the middle-aged and the elderly, anesthesiologists are and will be increasingly involved in the management of these patients with the advent of more aggressive surgical and other therapies. The principal authors, both consultant anaesthetists at a major referral center for comprehensive cancer therapy, are well qualified in the subject. Some terms used in this British book such as theatres (operating rooms) and anaesthetist (anesthesiologist) may be a bit confusing to the American reader.

This book is essentially divided into two parts. The first part, though concise, provides a clear discussion of the range of procedures anesthesiologists may encounter in the anesthetic management of patients with malignant disease. A good review on the traditional and the most recent chemotherapeutic agents used for cancer patients, their side effects, and possible drug interactions with anesthetic agents is included. A good description and discussion of the different types of radiation therapy, their associated problems, and how anesthesiologists can help optimize these treatments are also given.

The second part of the book focuses on the management of general anesthesia and of intensive care for various

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surgical procedures. The authors make a reasonable but abbreviated attempt at an overview of the anesthetic technique involved in various surgical subspecialties, e.g., thoracic surgery and neurosurgery. Unfortunately, the discussion of subspecialty anesthesia management is too superficial to be of much use to the practitioner faced with a complex case, e.g., the discussion about sitting-position craniotomy is less than that contained in texts on neuroanesthesia. Many statements are outdated also. In Chapter 14, the authors incorrectly state that a low cardiac output exacerbates venous admixture. A decreasing cardiac output may have varying effects on Pa_{O_2}, but it has been observed that, in a wide range of pathological and physiological circumstances with the exception of regional pulmonary atelectasis, a reduction in cardiac output causes an approximately proportional reduction in venous admixture. In the same chapter, the authors state that fiberoptic bronchoscopy is hazardous in the presence of severe upper airway obstruction and argue that intravenous induction and paralysis with suxamethonium will allow a rigid bronchoscope to be passed safely through an externally compressed trachea. Those statements are at variance with the practice common in America of securing the airway before administering a relaxant in cases where the airway is compromised.

The sections on monitoring are also outdated. Not enough emphasis is placed on the necessity of pulse oximetry, especially during one-lung anesthesia, and the importance of capnography in assessing ventilation when patients are monitored from a distance. In Chapter 11, the authors state that monitoring of electrocardiogram, blood pressure, and pulse oximetry are desirable in the "induction room," but if these monitors are not available, one is told to fall back on the arts of observation of skin color, respiratory pattern, and pulse palpation. Although pulse oximetry and capnometry may be just "desirable" in England, in America in 1990 they are standard!

In conclusion, the first 10 chapters about malignant disease and its relation to anesthesia are informative. Whether the chapters that discuss anesthesia management for patients with malignant disease are particularly useful is debatable. I would turn to other references for the latter.

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Pain Management in Emergency Medicine

P. M. Paris and R. D. Stewart. East Norwalk: Appleton & Lange, 1988, 526 pp, $65.00.

There has long been a need for a textbook covering the management of pain in the emergency setting. This reviewer was eagerly looking forward to reading this book in the anticipation that experts in emergency medicine would provide practical and clinically relevant vignettes that would promote excellence in those beginning their training. The first two chapters seemed to fulfill those expectations. Unfortunately, the remainder of the book did not, for major portions of the text are grossly inaccurate and dangerously misleading.

The chapter on the use of ketamine for dissociative sedation in the emergency room contains incorrect statements that could easily lead the well-intentioned novice down a pathway to catastrophe. The discussion begins with the use of 0.5 to 1 mg intramuscular doses of ketamine as a calming technique, then quickly evolves to the intravenous use of ketamine with benzodiazepines as adjuvants. They cite an example of the use of "diazepam (10 to 20 mg) and ketamine (1 to 2 mg/kg) in 52 patients undergoing painful surgical procedures in the emergency department." The rate and route of administration is not specified. Failure to mention the possibility of regurgitation, aspiration, or respiratory depression and the need for monitoring patients or airway protection are glaring omissions. The reference quoted states "It is unwise for the doctor giving the drug to also be the operator except in a dire emergency. The administrator must be able to pass an endotracheal tube in an emergency, and be capable of instituting any resuscitation that might be necessary." There is no mention of these potential problems in the book. Instead, they expand on the notion that this is a safe method of sedation in regular emergency room patients by quoting other studies out of context, ones that do not involve emergency room patients.

The physician who has had extensive experience in the use of ketamine may easily gloss over this chapter without noticing the lack of discussion about the inherent dangers of ketamine. The inexperienced clinician might easily be swayed to use the doses mentioned with no regard for patient selection, monitoring, or the availability of resuscitation equipment and personnel. The doses suggested in the text would induce a state of general anesthesia in most patients if given as an intravenous bolus. Without ventilatory support, some of these patients could easily suffer hypoxic damage or death.

The chapter "Pain Control in Prehospital Care" has similar deficiencies. The use of morphine, nitrous oxide, methoxyflurane, enflurane, and ketamine by paramedics are all mentioned but are inadequately discussed from the standpoint of safety and efficacy.

Scattered throughout many otherwise well-written chapters are typographical errors and incorrect information that could lead to patient injury or improper treatment. In the checklist that delineates the treatment of local anesthetic systemic toxicity, the need to oxygenate and ventilate a patient convulsing from a local anesthetic overdose is not presented in a clear-cut manner and may easily be overlooked. The inexperienced reader could easily perceive that the first action taken with the onset of a local anesthetic seizure is the administration of succinylcholine.

In the chapter on headache, they suggest that, when treating lumbar-puncture headache, "a dural patch consisting of autologous clot injected into the subarrachnoid space may be tried if symptoms are persistent and disabling." This novel approach is not documented with a reference that might allow the reader further review.

Some of the problems in *Pain Management in Emergency Medicine* could be attributed to the fact that there are 25 contributors. Most of the chapters, however, are written in an organized, informative fashion. Unfortunately, this textbook includes information that is not only inaccurate but also, at times, extremely dangerous. For these reasons this reviewer cannot recommend this book, which should be rewritten with major emphasis placed on accuracy and patient safety.

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Cardiopulmonary Resuscitation, Volume 17, Monographs in Anesthesiology

P. J. F. Baskett, ed. New York: Elsevier, 1989, 416 pp, $184.25.

The past 25 yr have seen a rapid proliferation in the basic science understanding, treatment protocol development, and training program organization of modern day cardiopulmonary resuscitation. In the literature much has already appeared that outlines the pathophysiology of cardiac arrest, the algorithms for its therapy, and the organization and implementation procedures for educational programs in cardiopulmonary resuscitation. New publications in this area, therefore, must measure up to what already exists in the current medical literature.

Cardiopulmonary Resuscitation, a Monographs in Anaesthesiology publication, is a new compilation of information on the understanding and treatment of cardiac arrest victims, and on training in life support for them. This monograph is organized in three sections: "General Clinical Aspects," "Special Clinical Aspects," and "Organizational Aspects." Everything is preceded by a chapter on the history of resuscitation, which in concise manner outlines the centuries of events that have brought us where we are today.

The "General Clinical Aspects" section considers the causes of cardiac arrest, the fundamental life support techniques, specific information on electrocardiogram diagnosis, defibrillator and pacemaker therapy, concepts of bioengineering and monitoring during cardiac arrest and cardiopulmonary resuscitation (CPR), pharmacological therapy, and post-CPR care. The review of these topics is generally inadequate. For example, (a) the pathophysiological considerations place undue emphasis on cardiac causes; (b) the presentation of basic life support follows the rather simplistic American Heart Association view of basic life support as a set of procedures that exclude the use of adjunctive equipment rather than looking at these techniques with or without adjuncts as temporizing measures to provide for oxygen deficits, with advance life support being the set of procedures with or without the adjuncts that allow restoration of spontaneous oxygen delivery on the part of the victim (1); (c) the consideration of implantable defibrillators describes the device's ability to sense ventricular fibrillation and/or ventricular tachycardia, but the explanation of how this is accomplished is incomplete; and (d) defibrillation energy requirements are incompletely considered, with factors such as the decrease in chest wall impedance with repetitive electrical shocks not mentioned.

The chapters on pharmacological resuscitation and post-resuscitative care are exceptions to the deficits of the other chapters in this section. The presentation on drug therapy is concise and well-organized, and provides the proper perspective as it reviews the principles of drug therapy as they deal with the oxygen deficits of cardiac arrest.

The "Special Clinical Aspects Section" is the strongest portion of this monograph and provides a problem-based learning approach to the management of cardiac arrest in specific situations, i.e., cardiac arrest in anesthesia and resuscitation after trauma, after near drowning, after poisoning in infants and children, and in the obstetric patient. Algorithms for management are provided in many of these chapters as "action plans." The action-plan treatment protocols and the text that accompanies them and explains the fundamental issues of therapy are the only sections that meet Dr. Campbell's recommendation in the forward for this monograph: "A comprehensive and authoritative text on the subject of cardiopulmonary resuscitation should be produced for medical practitioners and especially for those charged with training of undergraduates and postgraduates in the whole spectrum from immediate resuscitation to supportive follow up of survivors" (2).

The final section of the book on "Organizational Aspects of CPR Training" unfortunately provides little new information beyond what has been extensively provided in American Heart Association publications. Detailed information on training aids is provided in another chapter in this section. Although this information is undoubtedly useful for some individuals organizing CPR training programs, the amount of emphasis on this particular topic seems excessive.

The final two chapters on hospital-based resuscitation and the ethics of resuscitative care are welcome additions to the CPR literature, as these two topics have not previously been reviewed as fully as they might have been.

Cardiopulmonary Resuscitation is a recent addition to the many publications on life support principles, processes, procedures, and training. Although it is superficial in some areas and adds little to what already exists in the literature, there is considerable merit to the review of the special problems of cardiac arrest and their therapy. For this alone, the student of anesthesiology and critical care medicine would benefit from reading the material presented. If the reader studies the algorithms (action plans) for therapy and the supporting explanatory text with a view toward understanding the pathophysiology and rationale for therapy, this monograph will have served an important function in training physicians to recognize and deal with specific clinical situations. Such a problem-based learning approach is clearly a valuable way to learn CPR.

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Anaesthetic and Extracorporeal Gas Transfer

Keith L. Dorrington. Oxford: Clarendon Press, 1989, 274 pp, $75.00.

In a very real sense, gas transfer is a cornerstone of anesthesiology. In this addition to the Oxford Medical Engineering Series, Mr. Dorrington uses basic physical principles to explain many phenomena that practicing anesthesiologists take for granted.

The first chapter begins with an approximate derivation of the universal gas law using a "squash court model." Building on this foundation, the mathematical relationships governing oxygen and carbon dioxide transport within the body are derived. The text is straightforward and well illustrated; however, the derivation of the general form of the alveolar air equation seems circuitous. This relationship is then used to discuss the carriage of oxygen and CO_2 between the tissues and lung. Although not as thorough as the Rahn–Fenn monograph, I still found it informative and readable.

Chapter two is devoted to gas delivery systems for spontaneously breathing patients. The effects of changes in dead space and fresh gas flow on inspired oxygen concentrations and CO_2 elimination are clearly presented with simple algebraic equations and concise graphs. The relative merits of the Mapleson A through F partial rebreathing systems during spontaneous ventilation are then explored in depth. The text is well illustrated, and there is an interesting graphical analysis that demonstrates the superiority of the Mapleson A (pop-off near patient, fresh gas near bag) system. Of note is the fact that the entire discussion deals with partial rebreathing systems; the circle absorber systems commonly used in North America are relegated to a single paragraph.

Unfortunately, the continuity of the discussion is broken with an extremely complex derivation of the principles underlying the "Venturi" oxygen mask. By the time this reviewer reached equation 2.50, which shows the effect of back pressure on the F_{IO_2}:

$$\frac{\partial F_{IO_2}}{\partial p_e} = -\frac{1}{\rho u_0^2}\left\{\frac{0.8\left(\frac{a}{A'}\right)\left(1-\frac{a}{A'}\right)}{\left[\frac{a}{A'}+\frac{u_1'}{u_0}\left(1-\frac{a}{A'}\right)\right]^2}\right\}$$

$$\times\left\{\frac{1}{2\left(\frac{a}{A'}\right)\left(1-\frac{a}{A'}\right)\left(\frac{u_1'}{u_0}-1\right)-\frac{u_1'}{u_0}-\left[\frac{a}{A'}+\frac{u_1}{u_C}\left(1-\frac{a}{A'}\right)\right]\left(1-\frac{a}{A'}\right)\left(\frac{1-K^2}{K^2}\right)}\right\},$$

his ability to manage partial differential equations was sorely taxed. It is recommended that nonengineers accept the derivations and concentrate on the principles, which are shown graphically.

A similarly distracting digression appears in the "Anesthetic Vaporizers" chapter. After a straightforward but somewhat cumbersome derivation of the usual vaporizer relationships, Mr. Dorrington delves into the laws of thermodynamics to derive the Clausius–Clapeyron equation, which relates the vapor pressure of a liquid to its enthalpy of vaporization. After completing this derivation and assessing its accuracy, he resumes the discussion of vaporizers by addressing the ways in which modern, temperature-compensated vaporizers operate, and the physics underlying the effect of changes in gas flow on delivered anesthetic concentrations. Several interesting graphs compare the theoretical predictions with laboratory measurements.

In the following chapter, the discussion returns to breathing systems; this time gas exchange during controlled ventilation is addressed. The superiority of the Mapleson C and D systems (fresh gas inlet near patient) is clearly explained with a series of algebraic equations and graphs. However, the mechanical ventilators discussed are dissimilar to those with which American anesthesiologists are accustomed. The ventilators are primarily nonrebreathing devices that function by transiently occluding the free end of a "T-piece." The chapter concludes with a simplified evaluation of "axial dispersion" of flow within conducting airways; it is this nonuniformity of flow that makes it possible to provide adequate gas exchange during high frequency ventilation at low tidal volumes.

The final two chapters deal with the exchange of oxygen and carbon dioxide in extracorporeal lungs. The mathematical treatment of membrane oxygenators is extremely complex, involving second-order partial differential equations, multiple boundary conditions, and eigenfunctions. The solution to one set of equations occupies two full pages! Those who are unfamiliar with these concepts will probably gain maximum benefit from each subsection by reading the introductory text and looking at the graphical interpretation of the results (which show the correlation between the mathematically predicted values and those determined experimentally).

In conclusion, *Anaesthetic and Extracorporeal Gas Transfer* is an extremely rigorous treatment of selected concepts of gas delivery and transport. Unfortunately, the sequence of presentation leaves much to be desired, especially for nonengineers: unduly complex derivations are often interposed with more clinically relevant material. Those who are not comfortable with differential equations might prefer to skip several sections entirely. For those who relish a challenge, however, at the end of each chapter there are numerous problems (solutions provided), which made this reviewer feel as if he were back in engineering school.

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Anesthesia and Uncommon Diseases
(3rd edition)

J. Katz, J. L. Benumof, and L. B. Kadis. Philadelphia:
W. B. Saunders, 1990, 964 pp, $75.00.

Like its predecessors, the third edition of *Anesthesia and Uncommon Diseases* reviews in a well-organized and useful manner the anesthetic considerations in patients with a variety of medical diseases. As in the second edition published 8 years ago, not all of the chapters presented in this volume deal with conditions that are uncommon in present-day practice. For example, the sections dealing with the pregnant and the geriatric patient are very readable summaries of the alterations in physiology present in these populations and recommendations for their care that follow accepted guidelines.

Chapter organization is identical, with the exception of the insertion of two new chapters; one on liver disease and one on eye, ear, nose, and throat disorders. The information on liver disease is a much-expanded discussion of a topic presented in the previous edition. "Eye, Ear, Nose, and Throat Disorders" is short, but presents some interesting topics, such as the multiple medical and congenital causes of cataracts that may complicate an anesthetic procedure widely regarded as very basic.

Many chapters have had changes in authorship, and some of the new authors have completely rewritten their chapters (e.g., "Anesthesia for the Geriatric Patient," "Respiratory Diseases"). Others have chosen to edit and update chapters from the second edition, thus retaining much of the character of the original chapters (e.g., "Diseases of the Endocrine System," "Skin and Bone Disorders"). The new authors of "Gastrointestinal Disorders" have kept much of the previous chapter, but have added considerably to the introduction and background material.

Among the remaining chapters, two stand out. "Genetic and Metabolic Diseases" has considerably expanded discussions on basic genetics and genetic expression, carbohydrate and lipid metabolism and their disorders, and hypoglycemia. Much information has been included on anesthetic considerations for liver transplantation and extracorporeal shock wave lithotripsy, and management of patients with seizure disorders. Although by no means a complete treatise on these subjects, the chapter is extensively referenced and the references are listed numerically under topic headings. "Anesthesia for Patients with Behavioral and Environmental Disorders" presents much enhanced sections on cocaine, PCP, and marijuana abuse, reflecting the increased experience with victims of these drugs gained since the second edition was published. New information is added on pentazocine and ketamine addiction, as well as anesthetic considerations in patients inhaling nitrites. The discussions on intraoperative radiation therapy, and on the interactions between anesthetics, radiation doses, and chemotherapeutic agents (Bleomycin), are short but informative.

In summary, this new edition of a popular standard continues to be an organized, well-referenced, and quite readable text. Sufficient increases in knowledge and changes in anesthetic practice have occurred in the past 8 years to make this volume a useful update to the reference library of any practitioner or student.

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Durham, North Carolina

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The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Baumgardner WA, Reitz BA, Achuff SC. *Heart and Heart-Lung Transplantation*. Philadelphia: W.B. Saunders, 1990, 406 pp, $138.50.

Benjamin BND. *Diagnostic Laryngology, Adults and Children*. Philadelphia: W. B. Saunders, 1990, 177 pp, $95.00.

Feldman S, Harrop-Griffiths W, Hirsch N. *Problems in Anesthesia, Analysis and Management*. London: Heinemann Medical Books, 1989, 180 pp.

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Kirby RR, Taylor RW, Civetta JM. *Critical Care, Immediate Concerns*, Philadelphia: Lippincott, 1990, 784 pp, $44.95.

Oh TE, ed. *Intensive Care Manual*, 3rd ed. Boston: Butterworths, 1990, 700 pp, $39.95.

Taylor RW, Civetta JM, Kirby RR. *Techniques and Procedures in Critical Care*. Philadelphia: Lippincott, 236 pp, $34.95.

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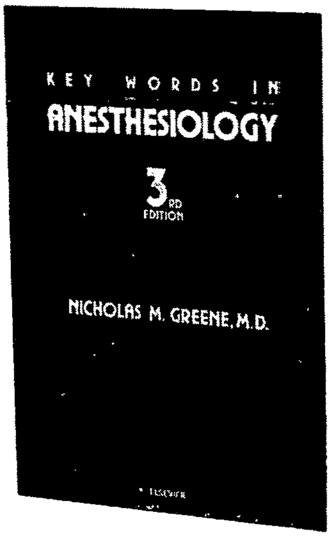

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434F/I

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436F/L

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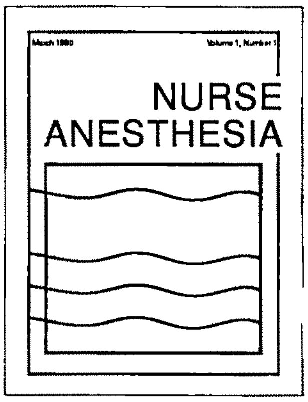

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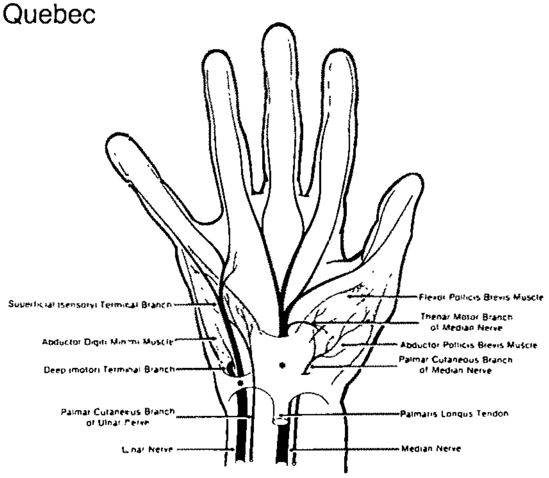

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Ulnar Nerve
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Median Nerve

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Anesthesia and Analgesia

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Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially atal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening n susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of weaning off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution

†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION: :

- When reconstituted with supplied bacteriostatic water for injection CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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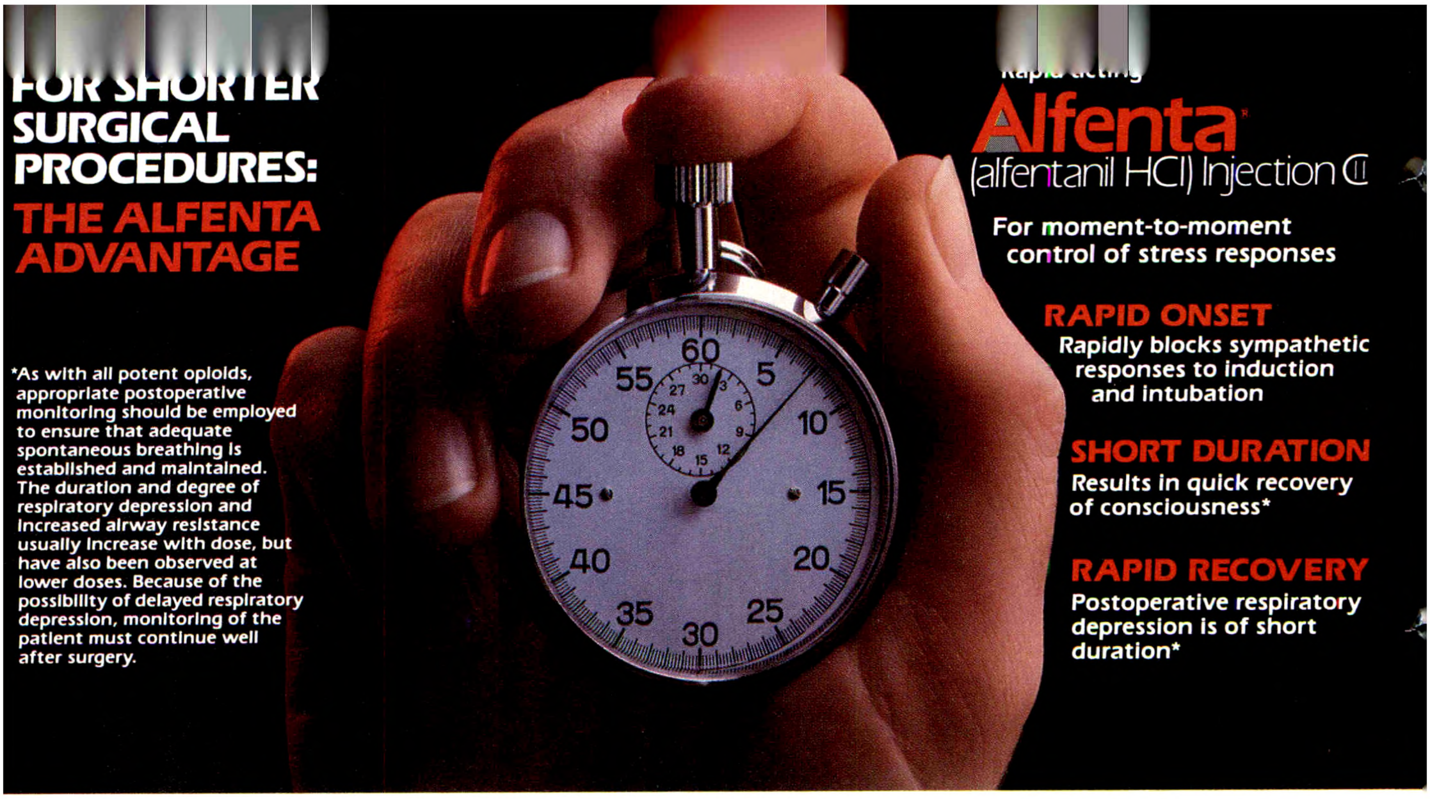

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Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

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DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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Anesthesia and Analgesia

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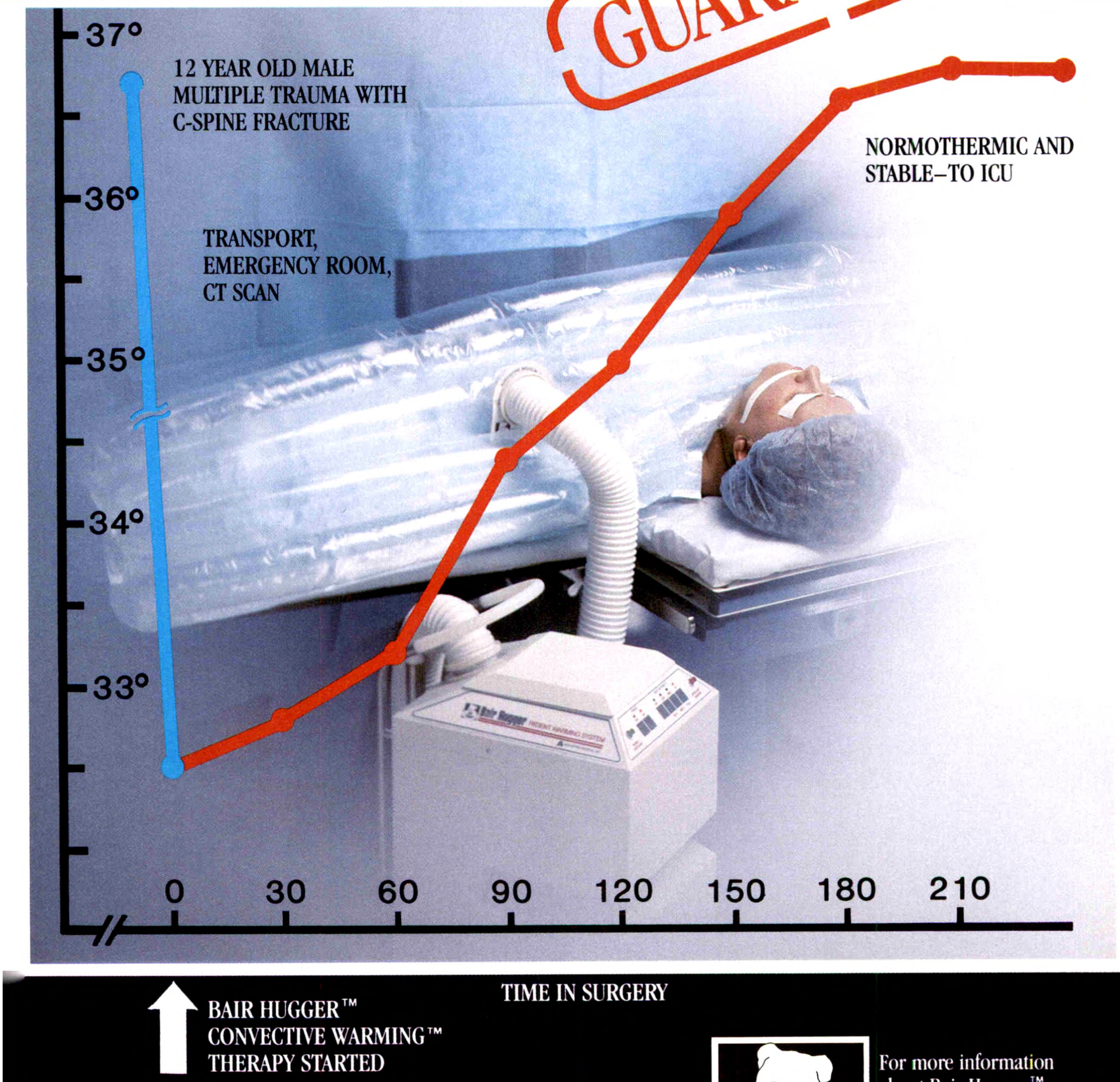

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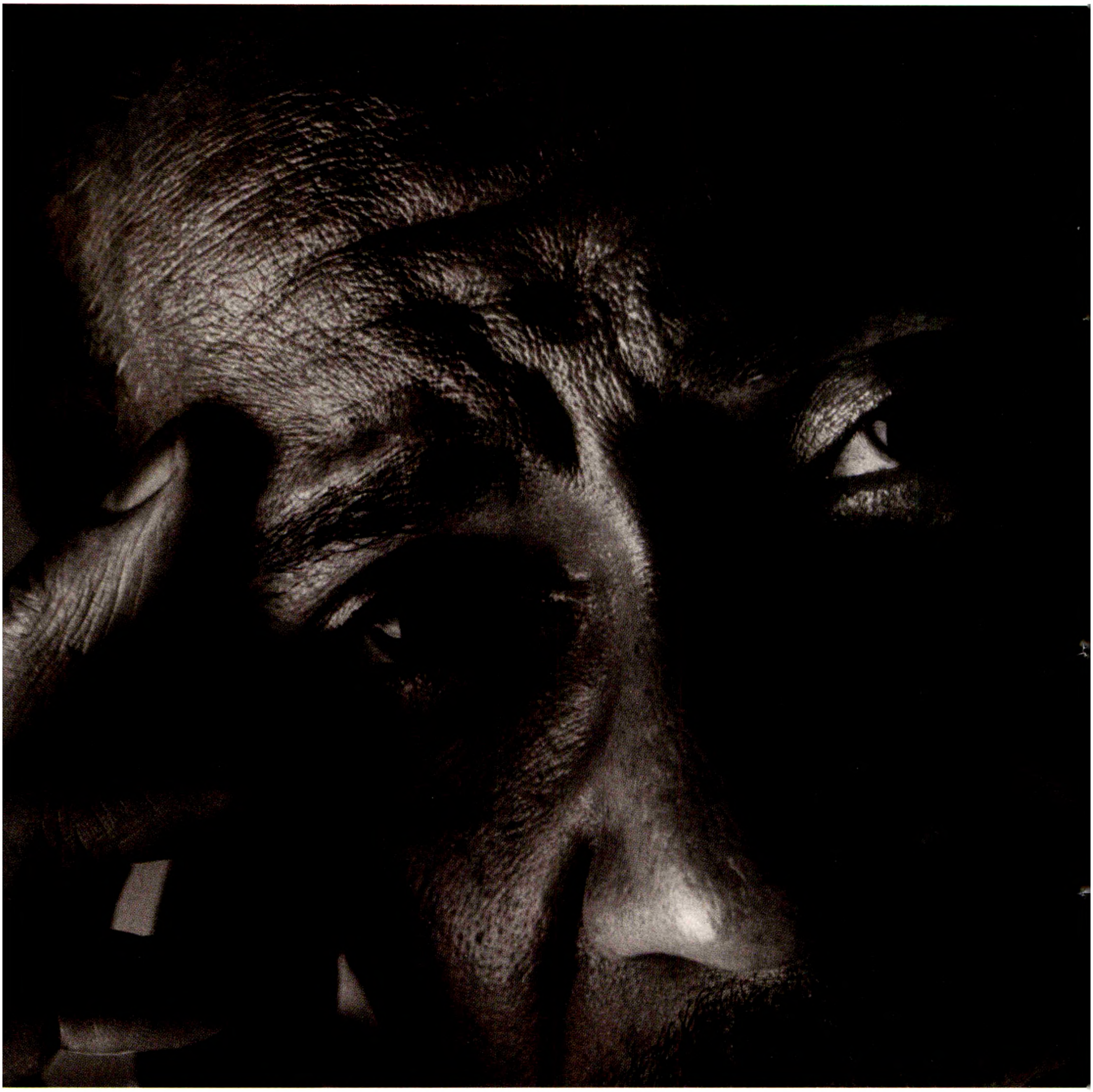

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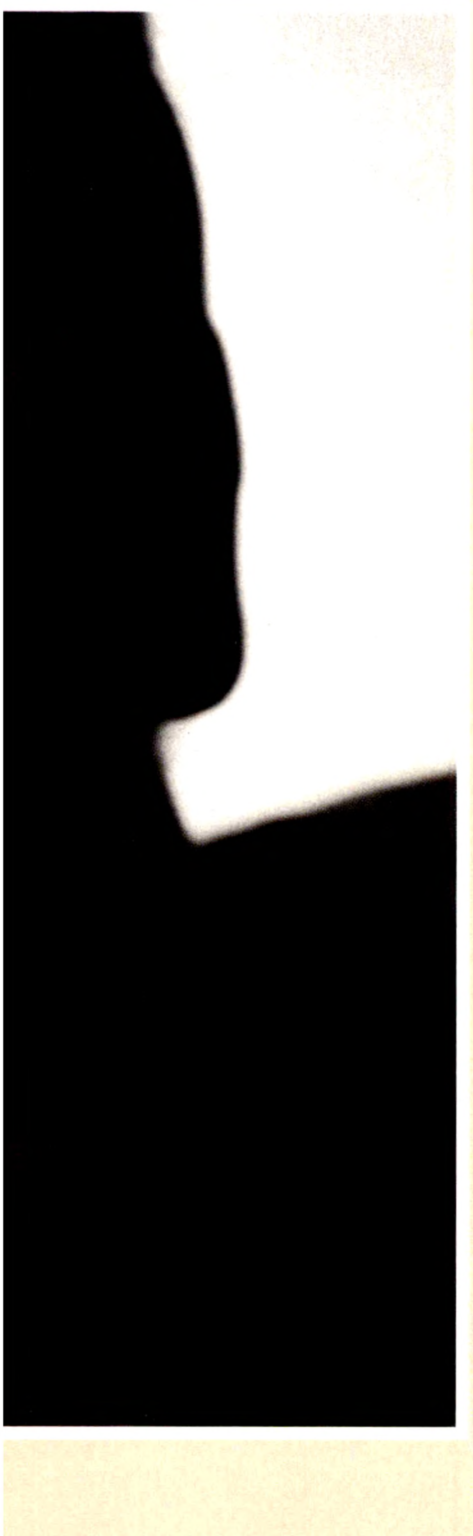

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References: 1. Hespan® Prescribing Information. **2.** Waters LM, Christensen MA, Sato RM: Hetastarch: An alternative colloid in burn shock management. *J Burn Care Rehabil* 1989;10:11–16. **3.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med* 1983;11:839–850.

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Brief Summary of Prescribing Information

CONTRAINDICATIONS

HESPAN is contraindicated in patients with known hypersensitivity to hydroxyethyl starch, or with bleeding disorders, or with congestive heart failure where volume overload is a potential problem. HESPAN should not be used in renal disease with oliguria or anuria not related to hypovolemia.

WARNINGS

Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of HESPAN. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count, hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/mL (normal 0.0–7.0 mg/mL) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS

The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing) bleeding due to hemodilution (see Warnings), and circulatory overload and pulmonary edema (see Precautions).

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion: HESPAN is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred.

Dosage in Leukapheresis

250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The safety and compatibility of other additives have not been established.

HOW SUPPLIED

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

HESPAN is supplied sterile and nonpyrogenic in 500 mL intravenous plastic infusion containers (NDC 0056-0037-44) and 500 mL intravenous glass bottles (NDC 0056-0037-05).

CAUTION

Federal (USA) law prohibits dispensing without prescription.

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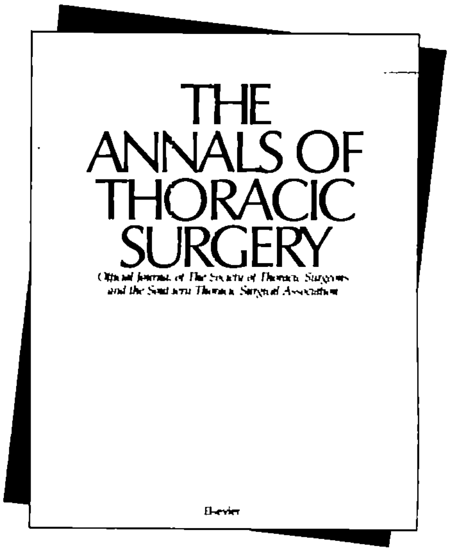

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β-Adrenergic Receptor Function Is Acutely Altered in Surgical Patients

Jean Marty, MD, Martin Nimier, MD, Catherine Rocchiccioli, MD, Jean Mantz, MD, Francis Luscombe, MD, Danielle Henzel, BS, Alain Loiseau, PhD, and Jean-Marie Desmonts, MD

MARTY J, NIMIER M, ROCCHICCIOLI C, MANTZ J, LUSCOMBE F, HENZEL D, LOISEAU A, DESMONTS J-M. β-Adrenergic receptor function is acutely altered in surgical patients. Anesth Analg 1990;71:1–8.

Catecholamine-induced desensitization of β-adrenergic receptors resulting in hyporesponsiveness to further stimulation has been frequently reported after an increase in endogenous catecholamines. To examine the possibility of β-adrenoceptor desensitization due to intraoperative adrenergic activation (surgical stress), the alterations of human lymphocyte β-adrenergic receptor density and affinity observed after anesthesia and surgery were studied using (-)^{125}I-iodocyanopindolol binding in 19 patients undergoing noncardiac surgical procedures with general anesthesia (thiopental, fentanyl, and halothane or isoflurane). In 13 patients, repeated determinations of plasma levels of norepinephrine and epinephrine showed an increase during the surgical procedure (norepinephrine +60%; epinephrine +60%); this change was not observed in the remaining patients. A significant postoperative increase in receptor density (B_{max} +25%) and a significant decrease of receptor affinity for isoproterenol (IC_{50} +22%) were found in the patients who experienced intraoperative adrenergic activation. By contrast, no significant change in β-receptor density or affinity was found in the patients who had normal intraoperative adrenergic activation. In addition, heart rate responses to the postoperative changes in plasma catecholamines (an index of cardiac sensitivity to agonist) were significantly attenuated in patients who experienced both intraoperative adrenergic activation and a decrease in affinity of β-receptor for agonist, suggesting hyporesponsiveness to β stimulation. We conclude that β-adrenergic receptors and, consequently, β-adrenergic responsiveness might be altered by perioperative adrenergic activation in surgical patients.

Key Words: SYMPATHETIC NERVOUS SYSTEM, β-ADRENERGIC RECEPTORS. RECEPTORS, β-ADRENERGIC.

Perioperative adrenergic activation related to surgical stress is considered to be a major contributor to cardiovascular complications after surgery, especially in patients with heart disease (1). However, several studies report a discrepancy between small changes in heart rate and blood pressure and the usually observed high levels of plasma catecholamines after surgery (2–5). These results may suggest a decrease in adrenergic responsiveness. Several mechanisms known to modify adrenergic receptor reactivity could be involved in the development of an alteration of β-adrenergic receptor function in surgical patients. However, the main factor implicated in regulation of adrenergic receptors is change in adrenergic activity. Persistent exposure to catecholamines results in lowered responsiveness of target cells to further stimulation by agonists through a phenomenon known as desensitization (6–12). Catecholamine-induced desensitization has been reported to occur after increases in endogenous catecholamines (8,11,13) or during chronic agonist therapy (9–11). It is associated with a decrease in β-receptor density when receptors are chronically exposed to a high level of catecholamines (9–11). Short-term regulation, consisting of a change in affinity of β-receptor for agonist has also been observed (8,14). Thus, this alteration might be expected after a surgical procedure because the perioperative period is often associated with marked and abrupt increases in adrenergic activity (2–5). It has been speculated that anesthetic techniques that in-

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hibit adrenergic activation (4,5) might avoid desensitization.

Perioperative changes in β-receptor density and affinity could be detrimental in patients with diminished β-receptor responsiveness to agonists such as patients with congestive heart failure (11,15,16) or older patients (17). In addition, acute changes might have several implications in the interpretation of studies performed in animals related to pharmacologic modifications of β-adrenergic receptors. Therefore, the present study was designed to assess the alterations of lymphocyte β-adrenergic receptor density and affinity related to intraoperative changes in plasma catecholamine levels in healthy surgical patients.

Methods

The study was approved by the local human investigation committee of our university. Nineteen patients, aged 18–60 yr, ASA physical status I, undergoing mild elective surgical procedure, were studied after they gave informed consent. None was taking any cardiac medications or drugs acting on the sympathetic nervous system. All fasted from midnight the night before surgery. Premedication consisted of lorazepam, 2.5 mg orally 60 min before induction of anesthesia. In all cases, anesthesia was induced with thiopental, 5 mg/kg intravenously, followed by succinylcholine, 1 mg/kg, to facilitate tracheal intubation. Anesthesia was maintained with N_2O (60% in oxygen) and fentanyl (3–8 μg/kg) plus halothane or isoflurane (inspired concentrations ranging from 0.5% to 1%). Doses of fentanyl and inspired concentrations of halogenated anesthetics were adjusted according to the usual criteria of anesthetic management by the attending anesthesiologist. At the conclusion of surgery, patients were brought to the recovery room. Tracheal extubation was performed after evaluation of consciousness, respiration, and hemodynamic parameters. Then nasal oxygen, 3 L/min, was administered to all patients.

Venous blood samples were withdrawn before induction and repeatedly during anesthesia (four times per hour) for the measurement of plasma concentrations of norepinephrine and of epinephrine by high-performance liquid chromatography (18). The absence of normal adrenergic activation was established when plasma norepinephrine and epinephrine levels during surgery (mean of all values obtained during surgery) increased <10% above preinduction levels (this value represents the coefficient of variation of the method used to measure plasma catecholamine concentration). Postoperative plasma concentrations of norepinephrine and epinephrine were determined 20 min after tracheal extubation when a stable clinical condition was achieved (no pain, no shivering). Heart rate (from electrocardiogram) and systolic and diastolic blood pressure values (using an automated pressure cuff or sometimes an arterial catheter) were obtained at the same times.

Density and affinity of lymphocyte β-receptors were determined by radioligand binding studies from blood samples (40 mL) collected before induction and at the time of recovery defined above. Heparinized whole blood was diluted with phosphate-buffered saline. The lymphocytes were then isolated using a Ficoll–Hypaque density gradient by centrifugation (600 *g* for 20 min) after removal of the plasma-saline layer, and the lymphocyte band was harvested by aspiration and resuspended in phosphate-buffered saline. After two washings and additional centrifugations, a pure preparation of lymphocytes was obtained (90%). The lymphocytes were then resuspended in ice-cold deionized water and broken up by ultrasonication. Aliquots were centrifuged at 40,000 *g* for 20 min at 4°C. The pellet was resuspended in 4 mL of 0.9% NaCl with 20 mM Tris–12.5 mM $MgCl_2$ and 1.5 mM ethylenediaminetetraacetic acid. Samples were frozen in liquid nitrogen until used for ligand studies, which were performed within 3 wk.

β-Receptor binding studies were performed according to a modification of the method of Feldman et al. (8). (-)^{125}I-iodocyanopindolol (ICYP) (Amersham Corp., 2200 Ci/mM) was used as radioligand. Lymphocyte membranes were incubated with ^{125}ICYP for 70–90 min at 37°C in a final volume of 250 μL containing 0.5 mM ascorbic acid, 60 μg/mL of bovine serum albumin, 0.03 mM phentolamine mesylate, 12 mM Tris-HCl (pH 7.4 at 37°C), 0.054% NaCl, 7.5 mM $MgCl_2$, and 0.9 mM ethylenediaminetetraacetic acid. For saturation binding curves, eight concentrations of ^{125}ICYP (5–166 pM) were used in each assay. For competition curves, one concentration of ^{125}ICYP (41 pM) was used in each assay. The reaction was terminated by addition of 10 mL of 0.9% of NaCl, 10 mM Tris-HCl, and 12.5 $MgCl_2$ followed by rapid filtration through Whatman GF/C filters. Each filter was then washed with an additional 10 mL of buffer. Radioactivity retained on the filter was determined in a gamma counter. All binding data were obtained in duplicate.

β-Adrenergic receptor density (B_{max}) was determined in saturation experiments. Nonspecific binding of ^{125}ICYP was defined as radioactivity bound that was not displaced by 0.1 mM of (-)isoproterenol. Specific binding of ^{125}ICYP was defined as total

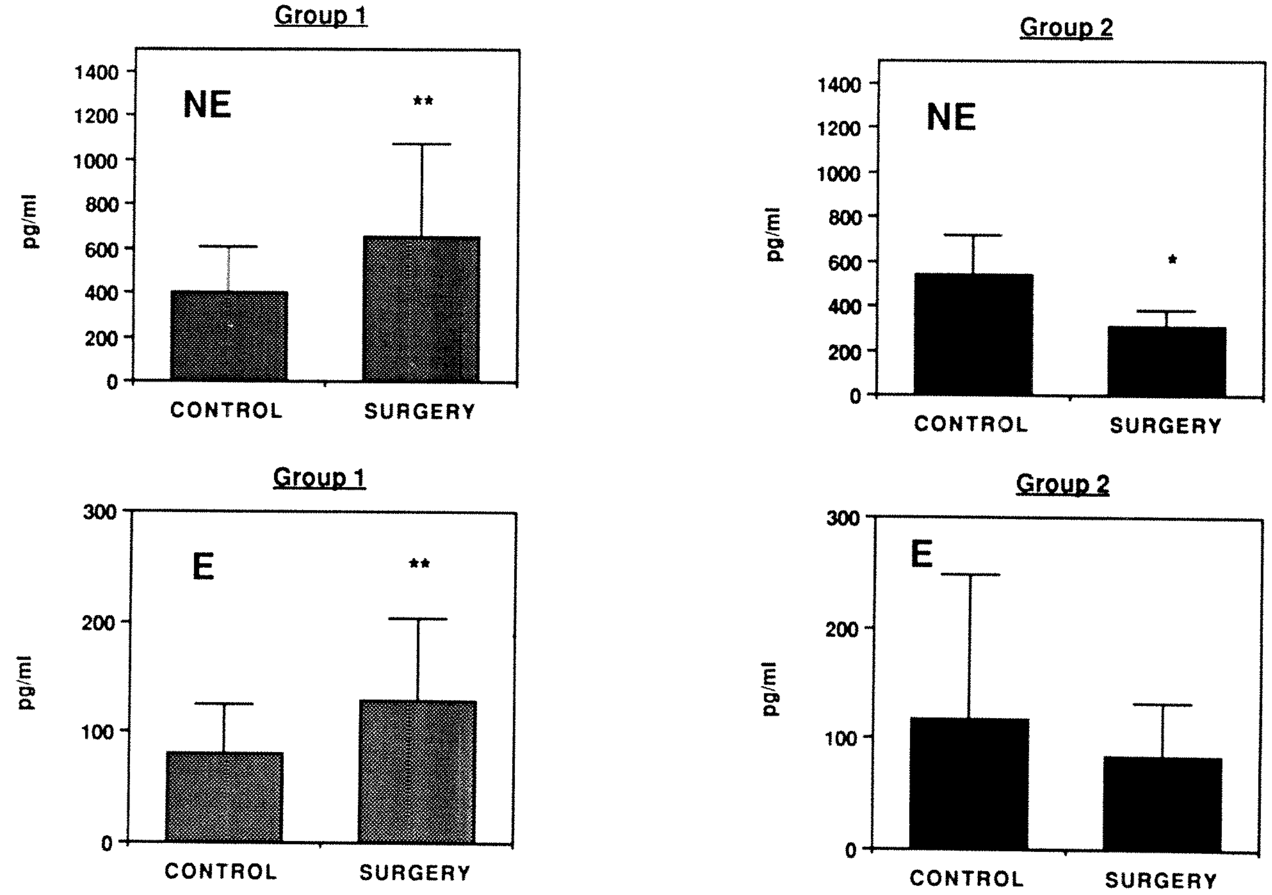

Figure 1. Plasma catecholamine levels before anesthesia (control) and during surgery (mean of values obtained from repeated measurements during surgery: four times per hour). In 13 patients (group 1) plasma catecholamine levels increased. In the remaining six patients (group 2), plasma catecholamine levels did not increase. $^{**}P < 0.01$, $^{*}P < 0.05$ versus preoperative levels.

radioactivity minus nonspecific binding. β-Receptor density (B_{max}, expressed in femtomoles per milligram of protein) was determined from experimental data by using nonlinear curve-fitting according to the law of mass action (19,20). Protein concentration was determined by the method of Lowry et al. (21). Receptor affinity for isoproterenol was derived from the data of competition experiments. The binding of ^{125}ICYP was determined at 13 concentrations of (-) isoproterenol ranging from 100 μm to 1 nM in the absence and presence of 5′-guanylylimidodiphosphate (0.1 mM). The IC_{50} for isoproterenol (concentration of isoproterenol required to displace 50% of specific binding) was determined from logit transformation of competition curves (22). Binding data were also analyzed by a nonlinear curve-fitting computerized procedure (20–23) assuming one or two affinity state models, according to the presence or absence of 5′-guanylylimidodiphosphate, to determine the dissociation constant of isoproterenol for the high (KH) and low (KL) affinity states and the proportion of receptor population (percentage of RH and RL) in each state. When only one affinity state was present, the dissociation constant of isoproterenol was assumed to be at low affinity (KL).

Statistical analysis was accomplished with nonpaired or paired *t*-test, analysis of variance with Bonferroni correction, and linear regression as appropriate. A *P* of <0.05 was considered to be significant.

Results

Data are presented as mean ± SD. Figure 1 shows that in 13 patients (group 1) an increase in mean plasma catecholamine concentrations (norepinephrine +60%, epinephrine +60%) was observed during surgery. This change was not transient as reflected by the time-course of individual modifications in plasma catecholamine levels in this group (as presented in Figure 2). In the remaining six patients (group 2), mean plasma norepinephrine decreased significantly, whereas mean epinephrine did not change significantly (Figure 1).

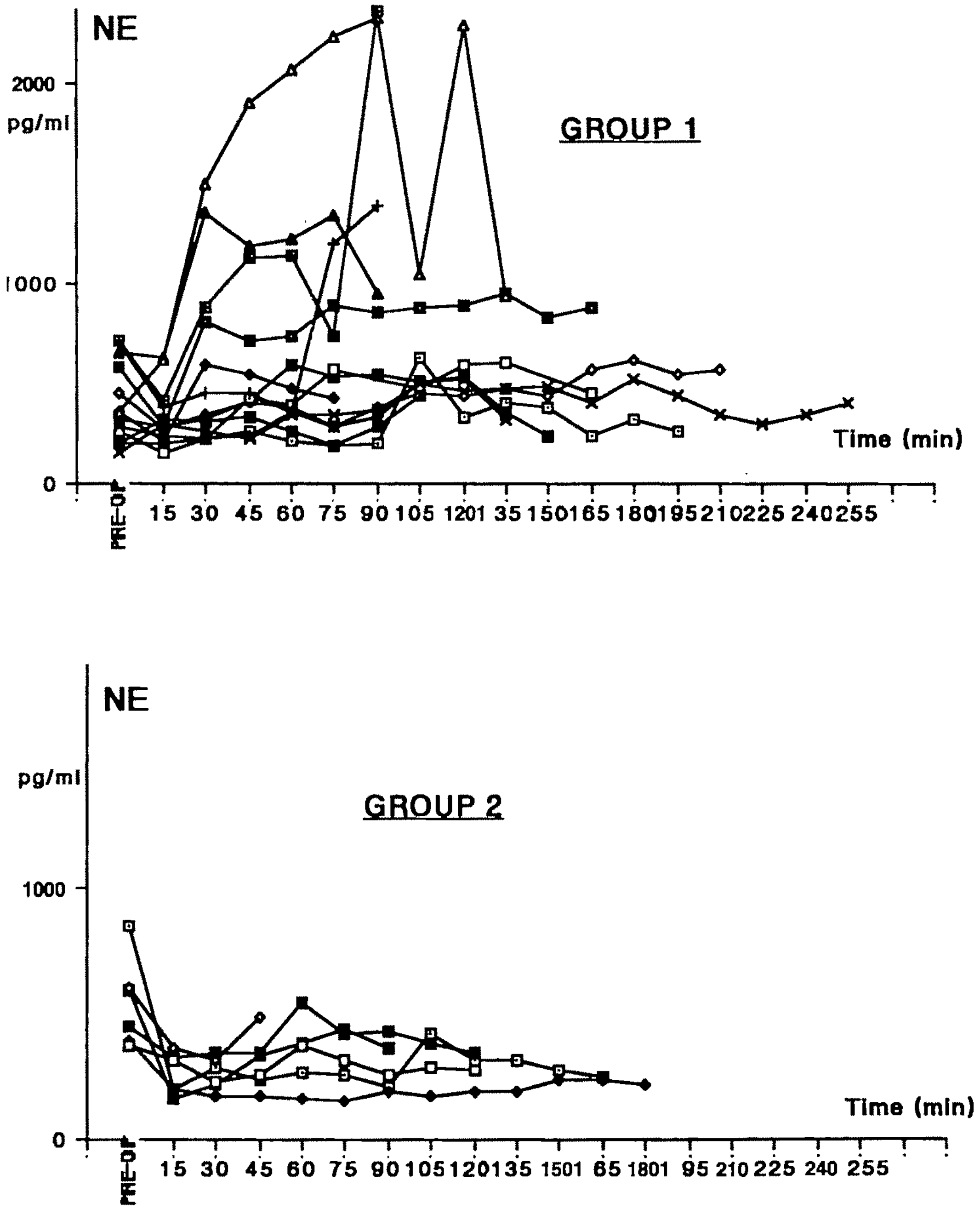

Figure 2. Changes in plasma norepinephrine levels during surgery in all patients. In group 1 the increase in plasma catecholamines is sustained except for a transient decrease just after induction of anesthesia. In group 2 there is a sustained decrease in norepinephrine levels.

Analysis of demographic data pertinent for the two groups showed that patients in group 1 were older than those in group 2 (Table 1). Also, preoperative heart rates were significantly higher in group 1 (Table 1). No significant difference was found between the two groups with respect to preoperative values of blood pressure, plasma concentrations of catecholamines, duration and type of surgery, and doses and types of anesthetics used (Table 1).

In the 13 patients with increases in plasma norepinephrine and epinephrine levels during the operation, there was a significant increase in β-receptor density (B_{max} +25%) (Figure 3). Competition binding curve analysis showed that curve-fitting was improved by assuming a two-affinity state in four of the 13 patients. After surgery, the two-affinity-states model best fit in only two patients. Comparison of KL obtained with this method showed a significant

Table 1. Demographic Data in the Two Groups (mean ± SD)

	Group 1[a] (n = 13)	Group 2[b] (n = 6)	P
Age (yr)	46.7 ± 10.5	30.8 ± 10.5	<0.05
Heart rate (beats/mm)			
Preoperative	80 ± 13	60 ± 8	<0.05
Postoperative	80 ± 7	79 ± 17[c]	NS
SBP (mm Hg)			
Preoperative	121 ± 16	117 ± 14	NS
Postoperative	131 ± 18	118 ± 20	NS
DBP (mm Hg)			
Preoperative	79 ± 11	70 ± 9	NS
Postoperative	81 ± 12	67 ± 10	<0.05
NE (pg/mL)			
Preoperative	403 ± 198	541 ± 179	NS
Postoperative	1470 ± 1106[c]	755 ± 175	NS
E (pg/mL)			
Preoperative	80 ± 44	118 ± 129	NS
Postoperative	228 ± 142[c]	161 ± 106	NS
Duration of surgery (min)	159 ± 57	122 ± 45	NS

SBP, systolic blood pressure; DBP, diastolic blood pressure; NE, norepinephrine (plasma levels); E, epinephrine (plasma levels); NS, not significant.

[a] Patients with intraoperative increases in plasma levels of catecholamines.

[b] Patients without intraoperative increases in plasma levels of catecholamines.

[c] $P < 0.05$ versus preoperative levels.

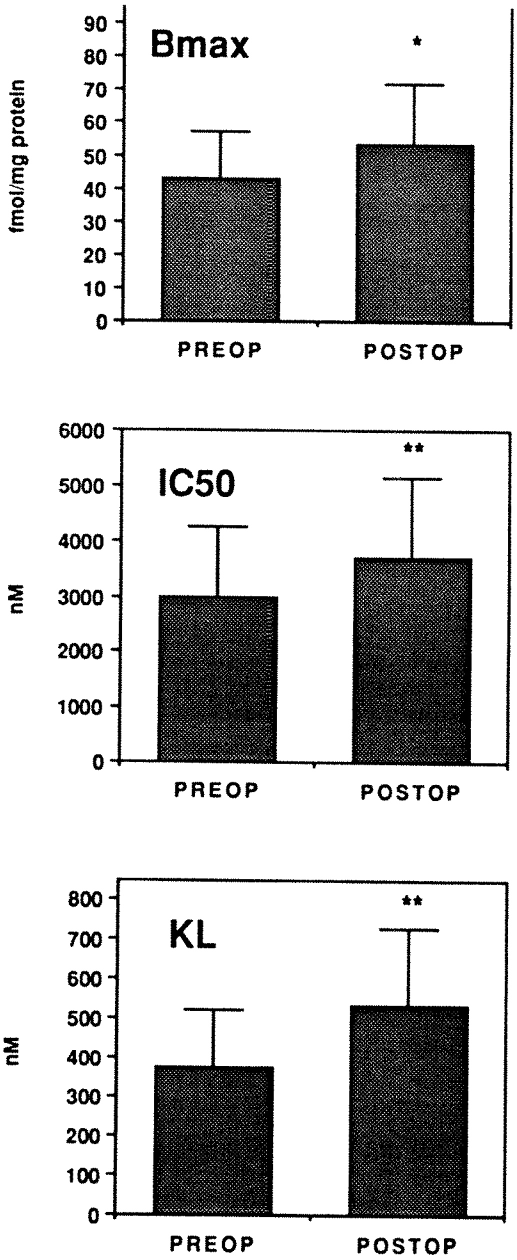

Figure 3. Binding data in the patients with increases in plasma catecholamine levels during surgery (group 1). Samples were obtained before anesthesia (preop) and during recovery (postop). B_{max}, density of receptors; IC_{50}, concentration of isoproterenol required to displace 50% of specific binding; KL, dissociation constant for isoproterenol. *$P < 0.05$, **$P < 0.01$ versus preoperative levels.

change after surgery (+50%) in these 13 patients (Figure 3). This alteration as well as the change in IC_{50} (+22%) (Figure 3) indicates that affinity of receptors for the agonist was reduced. By contrast, no significant change in β-receptor density or affinity was observed in group 2 patients (Figure 4).

Table 2 shows that the increase in heart rate observed postoperatively was significantly less in group 1 patients, whereas postoperative increases in plasma catecholamines were not significantly different in the two groups (although changes in postoperative norepinephrine levels seem more marked in group 1). This discrepancy suggests an alteration in cardiac sensitivity to catecholamines. However, no significant relation could be found between β-receptor binding data and heart rate changes in response to changes in plasma catecholamine levels.

Discussion

This study shows that β-adrenergic receptor function may be acutely altered in patients during and after surgery. An increase in plasma catecholamine levels was associated with β-adrenoceptor desensitization as assessed by the decrease in the affinity of receptors for agonists (increase in IC_{50} and KL). In addition, in patients who had increases in plasma catecholamine levels during surgery there was an increase in β-receptor density (as reflected by the change in B_{max}). By contrast, no significant modification was found in patients who did not experience these alterations in plasma levels of catecholamines.

The high baseline levels of epinephrine and nor-

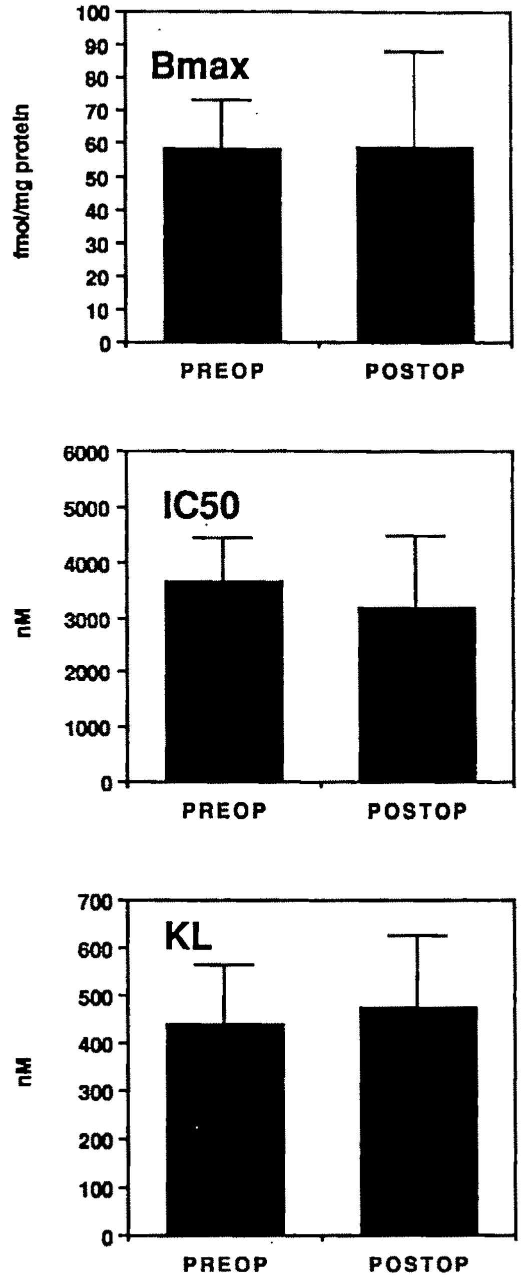

Figure 4. Binding data in the patients without increases in plasma catecholamine levels during surgery (group 2). Samples were obtained before anesthesia (preop) and during recovery (postop). See Figure 3 for abbreviations.

epinephrine, which were present in the two groups in the study, are commonly observed just before the induction of anesthesia (4). It is likely that they are related to preoperative anxiety. The significance of an increase in plasma levels of norepinephrine and epinephrine may be questioned because plasma concentrations of catecholamines are the net results of changes in (a) adrenergic activity in different organs and (b) metabolism or reuptake of catecholamines.

Table 2. Changes (Delta) in Heart Rate and Plasma Levels of Norepinephrine and Epinephrine Between Induction and Recovery (mean ± SD)

	Group 1[a] (n = 13)	Group 2[b] (n = 6)	P
Delta HR (beats/min)	0.38 ± 14.1	19.2 ± 14.3	<0.05
Delta NE (pg/mL)	1066 ± 983	213 ± 256	0.055
Delta E (pg/mL)	148 ± 154	43 ± 68	NS

HR, heart rate; NE, norepinephrine (plasma levels); E, epinephrine (plasma levels); NS, not significant.

[a] Patients with intraoperative increases in plasma catecholamine levels.

[b] Patients without intraoperative increases in plasma catecholamine levels.

However, it is generally accepted that stress, which increases adrenergic activity, results in an increase in plasma levels of catecholamines. This has been reported to occur frequently in surgical patients (2–5). In addition, the metabolic clearance of plasma catecholamines is unaffected by anesthesia and surgery (3). Therefore, the changes in binding data that were observed were associated with an increase in adrenergic activity that is likely to be related to surgical stress.

Brief physiologic increases in catecholamines result in detectable changes in agonist receptor interaction consisting of an increase in IC_{50} (8). Thus it is likely that a similar phenomenon occurred in our patients as increases in plasma catecholamine concentrations were associated with decreased receptor affinity to agonists.

The influence of age on the observed results should be discussed because alterations in leukocyte β-receptor affinity and in regulation of plasma catecholamine secretion have been reported with aging (17). However, these modifications have been described in patients older (55–74 yr) than those included in our study. In addition, baseline values of plasma catecholamine concentrations and binding data were not different between the two groups. Furthermore, aging is associated with an alteration in leukocyte β-receptor agonist interaction, whereas in the present study the modification of IC_{50} was only observed in the group with an increase in plasma catecholamine concentrations. Thus, it is not likely that the modest but significant difference in age between the two groups is involved in the observed changes.

Desensitization is usually associated with either a decrease in β-receptor density or with no change (6,10). Thus the increase in B_{max} that was observed in patients with adrenergic activation seems paradoxical. In fact, adrenergic stimulation is not the sole neuroendocrine response to surgery. Other hormones are involved in this response, particularly cortisol and ACTH (4,5). Previous reports have shown that corticosteroids can alter β-receptor sensitivity (24) and increase β-receptor density (25,26), probably by recruiting spare receptors. It can be speculated that perioperative increase in plasma cortisol levels induces a similar phenomenon in these patients; as we did not measure this hormone, we cannot verify this explanation. Further studies will be required to delineate all the mechanisms of the observations.

The possible influence of anesthetic techniques should also be discussed as some anesthetics have been reported to induce modifications in the affinity or density of some receptors (27–29). We have not observed changes in β-receptor density or affinity with thiopental and isoflurane, in vitro, at clinically relevant concentrations (unpublished data). Halothane has been shown to induce only very moderate alterations in human lymphocytes (29) or to produce no effect in the rat brain (30). Therefore, it is unlikely that the changes we observed were related to the anesthetic agents used. We cannot specifically address the influence of depth of anesthesia (which was left to the judgment of the attending anesthesiologist) on the current findings, except to speculate that anesthesia conducted at MAC-BAR depth theoretically will preserve receptor function.

The physiologic and pharmacologic consequences of the alterations observed in the density and affinity of lymphocyte β-adrenoceptors can only be speculated on because we did not examine directly β-adrenergic responsiveness. In addition, we do not know whether similar changes would be seen in β-receptors from other tissues (e.g., the heart). However, several studies have shown that β-receptors on circulating lymphocytes reflect β-receptors located on other target organ (31,32), at least when the changes in β-receptors are the consequences of systemic modifications of catecholamine levels. An increase in β-receptor density usually results in an enhancement in responsiveness except when the greater density of receptors is due to the recruitment of spare receptors (32). By contrast, a decrease in affinity for agonist, as observed in group 1, implies a hyporesponsiveness of target organs. This remains to be substantiated, but, in the present study, postoperative heart rate changes in response to postoperative adrenergic activation were markedly attenuated in patients who had a decrease in the affinity of their β-receptors for agonist. By contrast, in patients who did not experience a decrease in affinity for agonist, the cardiac sensitivity to endogenous catecholamines was not reduced. In fact, previous reports have already described alterations in the relationship between adrenergic activity and target organ responses postoperatively (3) or after stress (33). In particular, very high concentrations of catecholamines may be found during the perioperative period with only moderate changes in heart rate. However, no explanation has been offered to explain the mechanisms of these anomalies. This study is the first to report a change in affinity of β-adrenergic receptor that might account for adrenergic hyporesponsiveness observed in some patients. Further studies will be required to determine directly the relationship between changes in receptor function and alterations in responsiveness to agonists in surgical patients.

We conclude that adrenergic activation present during surgery can induce a decrease in agonist affinity of β-receptors. The clinical implications of these findings may be relevant in the management of patients with low density or low affinity of receptors (those with heart failure, older patients), patients in which an increased morbidity and mortality rate after surgery is observed. In addition, these findings may also have potential implications for the interpretation of data concerning β-adrenergic receptor activity in anesthetized animals or animals undergoing operations.

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Intestinal Hemodynamics During Laparotomy: Effects of Thoracic Epidural Anesthesia and Dopamine in Humans

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LUNDBERG J, LUNDBERG D, NORGREN L, RIBBE E, THÖRNE J, WERNER O. Intestinal hemodynamics during laparotomy: effects of thoracic epidural anesthesia and dopamine in humans. Anesth Analg 1990;71:9–15.

The effects of thoracic epidural anesthesia (TEA) and dopamine infusion (4 $\mu g \cdot kg^{-1} \cdot min^{-1}$*) on superior mesenteric artery blood flow (SMABF), the mesenteric arteriovenous oxygen difference (*AVD_{O_2}*), and the mesenteric venous lactate concentration were studied in nine patients before abdominal aortic reconstruction. Thoracic epidural anesthesia reduced SMABF, as measured by electromagnetic flowmetry, to 77% ± 8% (mean ± SEM) of control (*$P < 0.05$*), and mean arterial pressure to 46% ± 4% of control (*$P < 0.01$*). The mesenteric* AVD_{O_2} *increased from 27 ± 3 to 39 ± 6 mL/L (*$P < 0.05$*) and superior mesenteric venous lactate from 1.03 ± 0.11 to 1.60 ± 0.38 mmol/kg (*$P < 0.05$*); systemic* AVD_{O_2} *and lactate did not change. Dopamine had no significant effect on SMABF and mean arterial pressure before TEA. However, dopamine increased SMABF during TEA (from 77% ± 8% to 137% ± 21% of control;* $P < 0.01$*), returned mesenteric* AVD_{O_2} *to 27 ± 3 mL/L (*$P < 0.05$*), and elevated mean arterial pressure to 62% ± 4% of control (*$P < 0.05$*). It is concluded that the decrease in perfusion pressure during TEA reduces SMABF with resultant evidence of intestinal reductive metabolism. The intestinal blood flow during TEA was improved by dopamine.*

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—mesenteric blood flow. GASTROINTESTINAL TRACT, BLOOD FLOW—epidural anesthesia.

Thoracic epidural anesthesia (TEA) has been proposed as a useful adjunct to general anesthesia for abdominal aortic surgery (1). Besides reducing hypertensive, tachycardic, and endocrine-metabolic responses to surgery (2), epidural anesthesia has been found to improve the distribution of blood flow in the myocardium of the dog (3,4), to attenuate signs of myocardial ischemia, and to dilate stenotic coronary arteries in patients (5). Recent data also indicate that epidural anesthesia may decrease surgical morbidity (2,6,7). However, TEA usually induces such a pronounced cardiovascular depression that sympathomimetic vasopressors are needed (1,8). We have previously found in awake patients that infusion of dopamine during TEA promptly elevates the arterial pressure at doses as low as 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, mainly by increasing cardiac output (9).

From a clinical point of view it is evident that both the systemic and regional circulations are of great interest during aortic surgery, as patients needing this type of surgery generally have widespread vascular disease. This exposes them to an increased risk of organ hypoperfusion secondary to a lowered perfusion pressure. The intestinal circulation is of particular interest because profound intestinal ischemia is a serious postoperative complication with a high mortality (10–13). In the present study, we investigated the effects of TEA on the superior mesenteric arterial flow in patients scheduled for abdominal aortic reconstruction. Mesenteric oxygen extraction, systemic and mesenteric venous lactate concentrations, arterial catecholamine levels, and plasma renin activity were also measured. In addition, we studied the ability of dopamine to modify the changes induced by TEA.

Methods

The systemic hemodynamic effects of TEA and dopamine in the patients of this study have been the subject of a previous report, which included data

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from four additional patients (14). The investigation was approved by the Human Investigation Committee at the Medical Faculty, Lund University. Patients in whom preoperative angiograms showed stenosis of the main trunk of the superior mesenteric artery were not included in the study. Informed written consent was obtained from nine patients (three women, six men) with a mean age of 57 ± 3 yr (± SEM; range, 48–72 yr) and a mean weight of 74 ± 3 kg (range, 58–85 kg). The patients had no history of angina pectoris or myocardial infarction. All patients, ASA physical status II or III, were scheduled for abdominal aorto-bifemoral reconstruction due to obliterative vascular disease. Two patients were receiving antihypertensive treatment, one with verapamil and prazosin and the other with nifedipine. A third patient was being treated with salbutamol and theophylline for bronchial asthma. None of the drugs were taken on the day of surgery.

Anesthesia and Monitoring

The patients were premedicated with either 7.5–10 mg morphine IM ($n = 7$) or 10 mg diazepam rectally ($n = 2$) 45 min before arriving in the operating room. An epidural catheter was introduced 2–3 cm into the epidural space at the level of T7-8 or T8-9 via a median approach. No local anesthetic was injected epidurally at this point. A brachiocephalic vein was cannulated for the dopamine infusion (Intropin, Arnar Stone, McGaw Park, Ill.). Anesthesia and muscular relaxation were induced with 0.2–0.5 mg fentanyl, 175–450 mg thiopental, 100 mg succinylcholine, and 3–12 mg pancuronium. During laparotomy, anesthesia was maintained with 0.5%–2.0% enflurane and 65% nitrous oxide in oxygen. However, enflurane was discontinued before the first splanchnic vascular measurements were made. Diazepam, 2.5–5 mg IV, was repeatedly given during the investigation to prevent awareness. Normoventilation was maintained with a Servo 900B ventilator (Siemens-Elema, Sweden) and end-tidal CO_2 was monitored with a Siemens-Elema CO_2-analyser 930. The minute volume was unchanged during the investigation. Ringer's acetate solution was infused at a rate of 5–7 mL·kg^{-1}·h^{-1}.

Systemic arterial pressure was measured via a 1.20-mm radial artery cannula connected to an HP 1280 C pressure transducer (Hewlett-Packard). A pulmonary artery catheter (IL 44166 7F, Instrumentation Laboratory) was inserted through the right internal jugular vein. Cardiac output was measured by thermodilution with an IL 701 cardiac output computer (Instrumentation Laboratory) and measured in triplicate with 10 mL of iced 5% glucose as indicator.

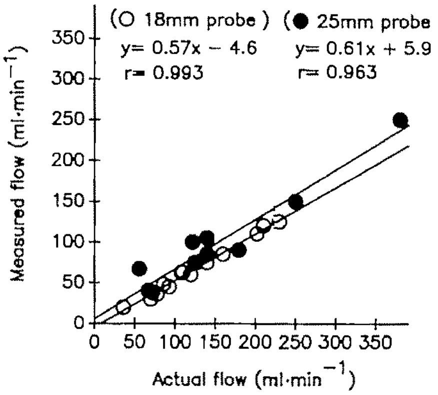

Figure 1. Calibration curves for the two electromagnetic flow probes.

After laparotomy, the superior mesenteric vein was cannulated with an 8F cannula. The superior mesenteric artery was dissected close to its origin. A precalibrated 18-mm ($n = 8$) or 25-mm ($n = 1$) electromagnetic flow probe was attached around the vessel so that adequate vessel contact was achieved during the measurements. The probe was connected to a Cme Cliniflow Blood Flow Meter (model 601 D, Carolina Medical Electronics), and zero adjustment was done by briefly clamping the vessel. This procedure was performed before the investigation and was repeated if the probe had been disconnected. The intestinal blood flow measurement was obtained after approximately 3–5 min of steady pulsatile flow to avoid the possible influence of vasoconstriction or reactive hyperemia. Previous in vitro calibration of the two probes, using segments of human saphenous vein perfused by whole blood, gave a high linear correlation between the reference flow and the electromagnetic flow meter, and the intercepts of the regression lines were small (Figure 1). This suggested that the instrument gave satisfactory relative measurements. However, the slope of both regressions were markedly different from unity. Absolute values were therefore considered less reliable and, where presented, were corrected according to the calibration equations.

Recording of electrocardiogram (lead CS_5), cardiac output (CO), heart rate (HR), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and superior mesenteric artery blood flow (SMABF) was performed on a Mingograf-81 recorder (Elema-Schönander, Sweden). Both unfiltered pressure curves and damped curves representing mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) were obtained (15). Systemic vascular resistance (SVR) and pulmonary vascular resistance were calculated as (MAP − CVP)/CO and (MPAP − PCWP)/CO, respectively. In humans, the portal venous pressure has been reported to be 8 ± 0 (16) and 11 ± 1 mm Hg (17), i.e., somewhat greater than the central venous pressure. Because the portal venous pressure was not measured in the present study, mesenteric vascular resistance (MVR) was calculated as MVR = (MAP − CVP)/SMABF.

Measurement Protocol

In addition to the stages outlined below, MAP and HR were measured approximately 5 min before the induction of general anesthesia.

The control measurement (CTRL) was made when enflurane had been discontinued for at least 10 min. The measurement sequence was kept short because of temporary hypertension in some patients.

The second measurement (DOP) was performed at the end of a 15-min dopamine infusion at 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which was then terminated.

The third measurement (TEA) was made approximately 30 min after establishing TEA with 10–12 mL of mepivacaine (Carbocain, 20 mg/mL, Astra, Sweden) followed by a continuous infusion at 10–12 mL/h. To maintain CVP and PCWP at the same levels as during CTRL, approximately 1000 mL of Ringer's acetate solution and 500 mL of 5% albumin were infused during induction of TEA.

The fourth measurement (TEA + DOP) was performed 15 min after reintroducing the dopamine infusion.

Laboratory Analyses

Blood samples were withdrawn from the radial artery, the superior mesenteric vein, and the pulmonary artery in connection with the hemodynamic measurements. Blood gas analyses were performed with an IL 413 blood gas analyzer (Instrumentation Laboratory). Oxygen saturation and hemoglobin contents were assessed with an OSM-2 analyzer (Radiometer, Denmark). The systemic and mesenteric arteriovenous oxygen differences ($AVDo_2$) were calculated according to standard formulas. The estimated systemic oxygen uptake was calculated as $AVDo_2 \times CO$. Blood glucose, lactate, and pyruvate concentrations were determined with specific enzymatic and fluorometric methods and expressed as millimoles per kilogram wet weight (18). Arterial norepinephrine, epinephrine, and dopamine plasma levels were determined using high-performance liquid chromatography with electrochemical detection (19) with an interassay sensitivity of 5%–15% depending on the catecholamine content in each sample. The reference values with this method are norepinephrine, 170–680 pg/mL; epinephrine, <75 pg/mL; and dopamine, <60 pg/mL. The plasma renin activity in radial arterial blood (n = 8) was analyzed with a radioimmunoassay method with an 8% intraassay and a 13% interassay coefficient of variation (20). The renin reference value was 1.34 ± 0.27 $\mu g \cdot L^{-1} \cdot h^{-1}$. The plasma mepivacaine concentration in radial arterial blood was determined with a gas chromatographic and mass spectrometric method at Astra Alab AB, Södertälje, Sweden.

Statistics

Repeated measures analysis of variance and multiple pairwise comparisons by calculating least-square means were performed by utilizing the SAS computing system version 5.18 (SAS Institute, Cary, N.C.). Comparisons were made between such preanesthetic data as were available and CTRL, CTRL and DOP, CTRL and TEA, and between TEA and TEA + DOP, respectively. The results are expressed as mean ± SEM. P-values of <0.05 were considered significant.

Results

During the study, the range of pulmonary arterial blood temperatures was 35.1°–36.2°C. $Paco_2$ ranged between 4.7 ± 0.2 and 5.2 ± 0.2 kPa during the measurements. In all patients MAP, HR, and the plasma concentrations of norepinephrine and epinephrine decreased 30 min after the epidural injection of mepivacaine. As a result of the volume loading during the induction of TEA, the arterial hemoglobin concentration decreased from 128 ± 5 to 114 ± 3 g/L. The plasma mepivacaine concentration was 2.0 ± 0.2 and 3.3 ± 0.4 μg/mL 0.5 and 1.5 h after the epidural injection. During the recovery period, the patients did not show any signs of adverse myocardial or intestinal reactions.

The plasma dopamine concentrations were similar during the two periods of dopamine infusion (Table 1). At CTRL, both norepinephrine and epinephrine were above the normal range. Although being markedly reduced by TEA, the levels of norepinephrine and epinephrine were not significantly altered by the dopamine infusion. No significant changes in the plasma renin activity were found (Table 1).

Table 1. Arterial Plasma Catecholamine Levels and Plasma Renin Activity

	CTRL	CTRL + DOP	TEA	TEA + DOP
Norepinephrine (pg/mL)	787 ± 82	900 ± 95	412 ± 63[a]	568 ± 79
Epinephrine (pg/mL)	481 ± 150	497 ± 185	251 ± 140[a]	231 ± 167
Dopamine (ng/mL)	0.2 ± 0.04	88 ± 7[a]	1.5 ± 0.4[a]	95 ± 9[b]
Renin activity ($\mu g \cdot L^{-1} \cdot h^{-1}$)	1.0 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	1.0 ± 0.1

CTRL, control measurement; DOP, dopamine infusion; TEA, thoracic epidural anesthesia.
Assessment of changes was performed as follows: CTRL vs CTRL + DOP, CTRL vs TEA, and TEA vs TEA + DOP.
[a] Significant change in relation to CTRL ($P < 0.01$).
[b] Significant change in relation to TEA ($P < 0.01$).

Mean arterial pressure and HR were elevated above preanesthetic levels at CTRL (MAP: 140 ± 9 vs 117 ± 8 mm Hg, $P < 0.01$; HR: 77 ± 4 vs 68 ± 2 beats/min, $P < 0.05$). The establishment of TEA decreased MAP to 65 ± 5 mm Hg and HR to 63 ± 3 beats/min (Figure 2). Dopamine did not increase MAP before TEA, but clearly did so after the establishment of the regional anesthesia (from 65 ± 5 to 86 ± 6 mm Hg, $P < 0.05$). During the study no significant changes were observed in CVP (range: 5 ± 1 to 8 ± 2 mm Hg), PCWP (10 ± 2 to 12 ± 2 mm Hg), MPAP (15 ± 2 to 20 ± 3 mm Hg), and pulmonary vascular resistance (1.3 ± 0.5 to 1.8 ± 0.4 mm $Hg \cdot L^{-1} \cdot min$).

At CTRL, CO was 4.4 ± 0.3 L/min and SMABF was estimated to be 288 ± 77 mL/min. Epidural anesthesia caused no significant decrease in CO, but reduced SMABF by 23% ± 8% (Figure 2). Both SVR and MVR decreased markedly. Dopamine significantly increased CO both before and during TEA (from 4.4 ± 0.3 to 5.5 ± 0.6 L/min and from 3.8 ± 0.3 to 4.7 ± 0.5 L/min, respectively), but increased SMABF only during TEA (from 77% ± 8% to 137% ± 21% of CTRL), concomitant with the increase in perfusion pressure. Both SVR and MVR remained unaltered by dopamine during TEA.

The arterial oxygen saturation during all stages was 96% with a SEM of 1% or less. At CTRL the mixed venous oxygen saturation was 71% ± 1%, and that in the superior mesenteric vein was 82% ± 2%. The lowest mixed venous and mesenteric venous oxygen saturation levels occurred during TEA (64% ± 1% and 73% ± 3%, respectively; $P < 0.01$ vs CTRL in each case). Both before and during TEA, infusion of dopamine decreased systemic $AVDo_2$, which essentially varied inversely with CO (Figure 2). Consequently, there was no significant variation in the estimated systemic oxygen uptake, which ranged between 194 ± 14 and 214 ± 13 mL/min. Also, mesenteric $AVDo_2$ varied inversely with flow, i.e., it increased during TEA, but subsequently decreased in response to dopamine (Figure 2). Generally, there were only minor differences between the arterial and the mixed venous lactate concentrations (range −0.14 ± 0.11 to 0.06 ± 0.07 mmol/kg). The induction of TEA did not alter the mixed venous lactate levels, but the superior mesenteric venous lactate level increased significantly (Figure 2), largely as a result of an extreme increase from 0.72 to 4.51 mmol/kg in one patient, a patient known from the preoperative angiograms to have an occluded inferior mesenteric artery. This patient had received β-stimulating medication (salbutamol) until the day before surgery. During TEA, MAP was 80 mm Hg, CO 2.65 L/min, and SMABF 69% of the control measurement. After the addition of dopamine, MAP was elevated to 85 mm Hg and CO to 2.83 L/min. Although SMABF was unaltered, the mesenteric venous lactate level decreased to 3.11 mmol/kg. Seven minutes later, MAP had reached 100 mm Hg in this particular patient. Smaller increases in mesenteric venous lactate contents were also seen in five other patients (from 0.60–1.37 to 0.83–1.68 mmol/kg), but only one of these had inferior mesenteric artery occlusion. Arterial blood glucose and pyruvate concentrations ranged between 8.2 ± 0.5 and 9.0 ± 0.4 mmol/kg and between 0.06 ± 0.01 and 0.10 ± 0.02 mmol/kg, respectively.

Discussion

Measurement of splanchnic blood flow with electromagnetic flow probes is a common technique in laboratory investigations (21). However, electromagnetic flowmetry in clinical studies has mainly been used in aortocoronary and peripheral arterial reconstruction. The technique appears only to have been employed occasionally on abdominal vessels (22–25). In the present study there was some uncertainty whether the electromagnetic flowmeter gave accurate absolute measurements, but in vitro calibration suggested that adequate relative blood flow measurements were obtained. As regards the blood sampling from the superior mesenteric vein, the cannula was directed toward the small intestine to avoid admix-

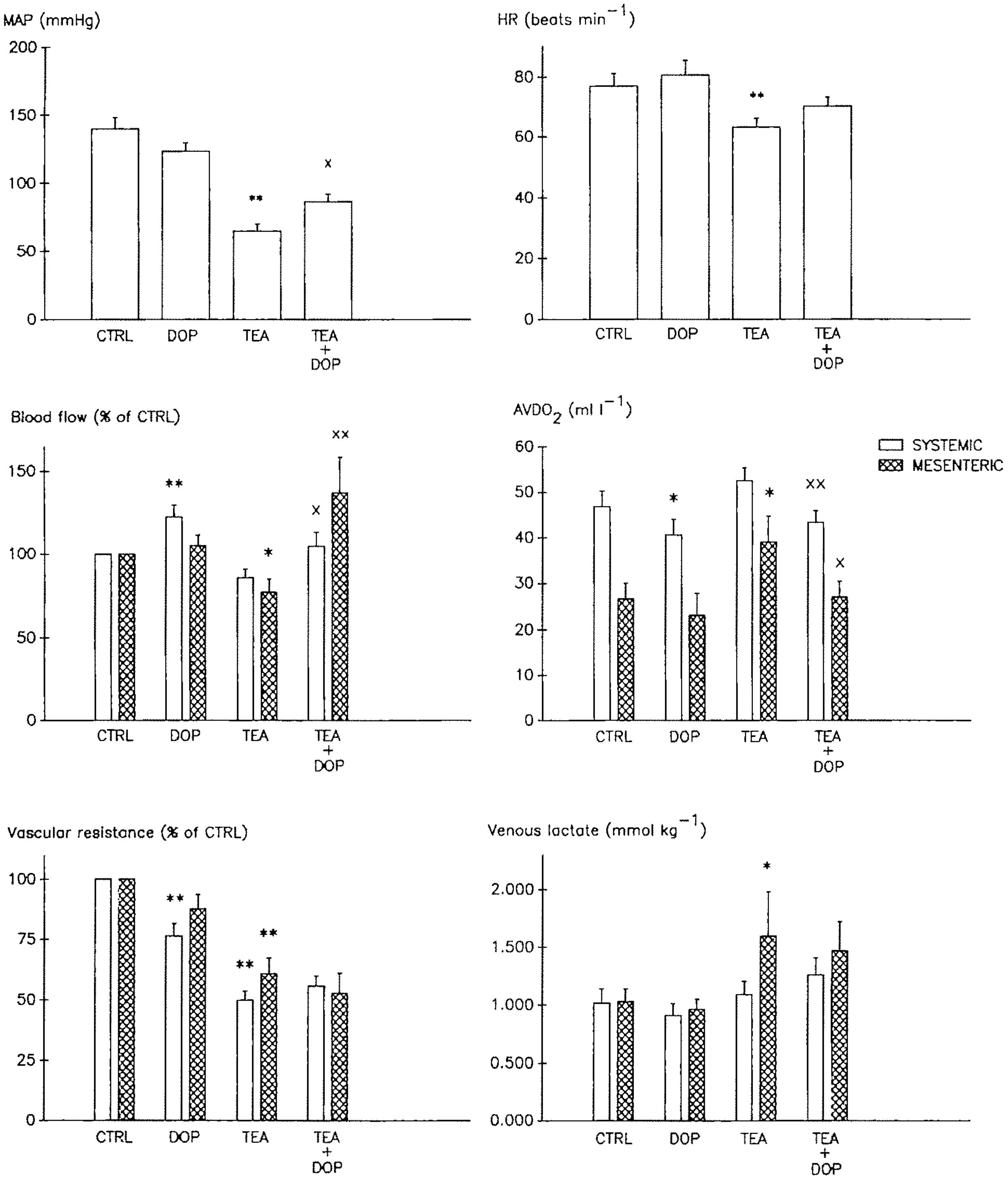

Figure 2. Changes in hemodynamics, oxygen extraction, and venous lactate during TEA and dopamine. MAP, mean arterial pressure; HR, heart rate; AVDo$_2$, arteriovenous oxygen difference. * and **, significant change in relation to CTRL; × and ××, significant change in relation to TEA ($P < 0.05$ and $P < 0.01$, respectively).

ture of blood from the spleen. Despite this precaution, the sampled blood might not exclusively have represented drainage from the superior mesenteric artery. It was thought, however, that the blood samples would give a satisfactory reflection of metabolic events in the intestine during changes in blood flow.

Before TEA, we found SMABF to be about 300 mL/min, whereas Norryd et al. (16), who used dye dilution in awake patients, found it to be 704 ± 21 mL/min. The difference may be due to methodology and also to the fact that our measurements were performed during surgery. However, our value agrees essentially with that of Ekeström et al. (24), who used the same technique as we did to study mesenteric arterial blood flow during abdominal aortic surgery. In the present study, the initial mesenteric $AVDo_2$ was approximately 27 mL/L, which is similar to previous findings during hepatic surgery (26).

Dopamine has repeatedly been reported to have vasodilatory properties in the intestine (27–29) secondary to activation of postsynaptic dopamine receptors. In the present study, intestinal vasodilation was not evident during intact innervation, although dopamine in this situation did reduce the SVR. That dopamine did not significantly reduce MVR before TEA is consistent with our previous findings in cats (30). One possible reason for the discrepancy between the results of our studies and those cited above could be that the effect of dopamine on the intestinal vascular resistance may depend on the preexisting level of sympathetic nervous activity. When the latter is high, the dopamine receptor activation may not be able to override the neurogenic vasoconstriction. Thus, the presence of elevated MAP and plasma norepinephrine and epinephrine levels in the present study during the control measurement suggests an initially increased sympathetic activity. The observed reduction in SVR during dopamine infusion supports the view that dopamine may have antihypertensive effects mediated by prejunctional dopamine receptors in the vasculature (31–34). Whether prejunctional dopamine receptors are also present in the human intestinal circulation is not clear (34), but our findings do not support their existence.

The hypotension, bradycardia, and decreases in plasma norepinephrine and epinephrine levels during TEA show that the reduction in sympathetic nervous activity was extensive. In addition, the plasma concentrations of mepivacaine that we observed made it unlikely that there were any important systemic effects of circulating drug (35). The decrease in SMBF during TEA was evidently caused by the 54% ± 5% reduction in perfusion pressure. The concomitant decrease in MVR, by about 40%, could be explained by intestinal vascular autoregulation. However, a TEA effect on the vascular sympathetic innervation may have contributed to this finding. We have previously observed that, in cats, epidural anesthesia increases intestinal blood flow if intestinal vascular perfusion pressure remains unchanged (30). In agreement with the present study, Greitz et al. (36), who studied the effects of high epidural anesthesia with bupivacaine in dogs, found a decrease in preportal vascular resistance when vascular perfusion pressure decreased; Johansson et al. (37), who studied laparotomized patients under epidural anesthesia, observed increases in intestinal blood flow simultaneously with a decrease in arterial blood pressure. In contrast, Kennedy et al. (38), who used epidural lidocaine in humans, found an increase in splanchnic vascular resistance despite an almost unaltered perfusion pressure. The choice of local anesthetic agent and the fact that Kennedy et al. measured hepatic venous blood flow rather than intestinal perfusion may have contributed to the different findings.

The increase in the mesenteric oxygen extraction during TEA, and the simultaneous increase in the mesenteric venous lactate concentration, which was very pronounced in one patient, suggest that the reduced intestinal perfusion pressure was not always well tolerated. The difference between systemic and mesenteric lactate levels was abolished by dopamine. At that time, mesenteric blood flow was approximately 140% of control, although dopamine did not increase the arterial pressure to the level seen before TEA. Thus, the combined effect of dopamine and TEA was that of a low intestinal vascular resistance in agreement with our previous laboratory findings (30). In addition, it seems unlikely that the plasma renin activity, which remained low and unchanged at all stages, affected our observations as regards the intestinal circulation.

In conclusion, TEA markedly reduced SMABF and increased the mesenteric arteriovenous oxygen difference. This was probably secondary to the reduction in perfusion pressure. Signs of transient intestinal reductive metabolism were present in one patient. During TEA, dopamine infusion elevated the intestinal blood flow, increased the systemic arterial pressure, and restored to normal levels oxygen extraction. Dopamine appeared to be essential during TEA for an adequate intestinal perfusion during abdominal surgery in patients with vascular disease.

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Mivacurium Infusion Requirements in Pediatric Surgical Patients During Nitrous Oxide-Halothane and During Nitrous Oxide-Narcotic Anesthesia

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BRANDOM BW, SARNER JB, WOELFEL SK, DONG M-L, HORN MC, BORLAND LM, COOK DR, FOSTER VJ, McNULTY BF, WEAKLY JN. Mivacurium infusion requirements in pediatric surgical patients during nitrous oxide-halothane and during nitrous oxide-narcotic anesthesia. Anesth Analg 1990;71:16–22.

We were interested in determining the infusion rate of mivacurium required to maintain approximately 95% neuromuscular blockade during nitrous oxide-halothane (0.8% end-tidal) or nitrous oxide-narcotic anesthesia. Neuromuscular blockade was monitored by recording the electromyographic activity (Datex NMT) of the adductor pollicis muscle resulting from supramaximal stimulation of the ulnar nerve at 2 Hz for 2 s at 10-s intervals. Mivacurium steady-state infusion requirements averaged 315 ± 26 $\mu g \cdot m^{-2} \cdot min^{-1}$ during nitrous oxide-halothane anesthesia and 375 ± 19 $\mu g \cdot m^{-2} \cdot min^{-1}$ (mean ± SEM) during nitrous oxide-narcotic anesthesia. Higher levels of pseudocholinesterase activity were generally associated with a higher mivacurium infusion requirement. During both anesthetics, younger age was associated with a higher infusion requirement when the infusion requirement was calculated in terms of $\mu g \cdot kg^{-1} \cdot min^{-1}$. This difference was not present when the infusion rate was calculated in terms of $\mu g \cdot m^{-2} \cdot min^{-1}$. There was no evidence of cumulation during prolonged mivacurium infusion. There was no difference in the rates of spontaneous or reversal-mediated recovery between anesthetic groups. After the termination of the infusion, spontaneous recovery to T4/T1 ≥ 0.75 occurred in 9.8 ± 0.4 min, with a recovery index, T_{25-75}, of 4.0 ± 0.2 min (mean ± SEM). In summary, pseudocholinesterase activity is the major factor influencing mivacurium infusion rate in children during nitrous oxide-narcotic or nitrous oxide-halothane (0.8% end-tidal) anesthesia.

Key Words: NEUROMUSCULAR RELAXANTS, MIVACURIUM—infusion. ANESTHESIA, PEDIATRIC—mivacurium.

Mivacurium chloride is a new nondepolarizing neuromuscular blocking agent with a relatively short duration of action. When administered in a dose of 0.25 mg/kg (approximately 2.5 times the ED_{95}) to children, mivacurium produces complete neuromuscular blockade in 1–2 min with complete spontaneous recovery within 15–30 min (1,2). Succinylcholine, the only short-acting relaxant now in clinical use, may be associated with numerous undesirable side effects in children (3–9). Because of its relatively rapid onset and short duration of action, mivacurium may be used as an alternative to succinylcholine in pediatric patients. Mivacurium has been compared with succinylcholine in adults (10). There are, however, age-related differences in bolus dose requirements (i.e., ED_{95} in mg/kg) and in the duration of action of mivacurium after bolus doses between children and adults (1). During nitrous oxide-oxygen-narcotic anesthesia, the ED_{95} in adults is 70 μg/kg, whereas the ED_{95} in children is 103 μg/kg. After a bolus of five times the ED_{50}, children recover to 5% neuromuscular transmission (T5) in 7 min, whereas adults recover to the same degree in 14 min.

In addition, potent inhalation anesthetics potenti-

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ate the neuromuscular blocking effects of mivacurium and, hence, decrease infusion requirements in adults (11,12). Therefore, we studied the infusion rate (IR) of mivacurium required to maintain neuromuscular blockade at 89%–99% in children during nitrous oxide-oxygen-halothane and nitrous oxide-oxygen-narcotic anesthesia.

Methods

Sixty-two children (ASA physical status I or II) between 2 and 10 yr of age undergoing elective surgical procedures requiring tracheal intubation were studied. The majority of patients underwent otorhinlaryngologic, dental, or plastic surgery. The study was approved by the Human Rights Committee of Children's Hospital of Pittsburgh; informed consent was obtained from a parent. No patient had a history of abnormal response to neuromuscular blocking agents. No patients received aminoglycoside antibiotics, antihistamines, or other drugs known to interfere with neuromuscular function within 48 h of the study. Blood was drawn immediately after induction of anesthesia for measurement of pseudocholinesterase activity and dibucaine number with propionylthiocholine iodide as substrate. The 59 patients who contributed to statistical analysis of infusion requirement had both pseudocholinesterase activity and dibucaine numbers in the normal range.

Patients underwent induction of anesthesia with halothane and nitrous oxide or with nitrous oxide and intravenous (IV) sedatives. The expressed preference and the ability of the patient to cooperate during induction of anesthesia influenced the choice of induction technique. If the patient received halothane during induction of anesthesia, halothane was continued throughout the anesthetic. Thus, patients were nonrandomly divided into two groups. One group (group H, $n = 21$) was studied during nitrous oxide-oxygen-halothane anesthesia; the other group (group N, $n = 38$) was studied during nitrous oxide-oxygen-narcotic anesthesia. Patients in group H were generally unpremedicated; one patient received oral diazepam (0.15 mg/kg). Patients in group N were premedicated with variable combinations of oral diazepam (0.1–0.2 mg/kg), intramuscular morphine (0.1–0.2 mg/kg) and scopolamine (6 μg/kg), and rectal methohexital (20–30 mg/kg).

In patients in group H, anesthesia was induced with nitrous oxide (70%) in oxygen (30%) and halothane (3%–5% inspired concentration). An IV catheter was inserted after induction of anesthesia, and an infusion of 5% dextrose in lactated Ringer's solution was begun. Atropine (10 μg/kg) was given intravenously before tracheal intubation. Tracheal intubation was accomplished without the aid of neuromuscular blocking agents or IV or translaryngeal lidocaine. After intubation the end-tidal halothane concentration was reduced to 0.8% ± 0.05%, nitrous oxide (70%) in oxygen (30%) was continued, and IV fentanyl (up to 6 μg/kg) was given if needed. End-tidal halothane concentration was measured using an infrared gas analyzer (Puritan-Bennett 222) and remained stable between 0.75% and 0.85% for at least 10 min before administration of mivacurium.

In patients in group N, nitrous oxide (70%–80%) in oxygen (20%–30%) was administered, an IV infusion of 5% dextrose in lactated Ringer's solution was established, and IV thiopental (4–10 mg/kg), diazepam (0.1–0.2 mg/kg), and fentanyl (2–6 μg/kg) were given as needed. Anesthesia was maintained with nitrous oxide (70%) in oxygen (30%) and fentanyl. In these patients the trachea was intubated after administration of mivacurium.

Normal minute ventilation as judged by the attending anesthesiologist, and normal body temperature were maintained intraoperatively. On the average, core body temperature increased about 0.5°C during the period of neuromuscular monitoring. The ulnar nerve was stimulated supramaximally (pulse width, 0.1 ms) using surface electrodes on the forearm with train-of-four stimuli (2 Hz for 2 s at 10-s intervals). The electromyogram of the thenar area approximating the adductor pollicis muscle was recorded using a Datex NMT monitor. The degree of neuromuscular blockade was described as percent of control; the height of the T1 response (first train-of-four response) after mivacurium administration was compared with the height of T1 before the initial bolus of mivacurium. The degree of neuromuscular blockade during recovery from infusion was referenced to the final baseline at the end of the study, when T4 equaled T1. Anesthetic administration was continued unchanged until T4 equaled T1.

An initial IV bolus of mivacurium was administered, and neuromuscular blockade and recovery were observed (1). A second bolus of mivacurium was then administered to establish complete neuromuscular blockade. The total amount administered ranged from 0.10 to 0.68 mg/kg per patient. An infusion of mivacurium (500 μg/mL in 5% dextrose in water) was begun, usually at a rate between 10 and 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ when neuromuscular transmission returned to approximately 10% of the initial baseline. The infusion was delivered with a Harvard infusion pump through a T-connector connected to the IV catheter. The IR was titrated to maintain neuromuscular blockade between 89% and 99% (i.e., 1%–11% neuromuscular transmission). The mivacurium infusion was continued for as long as required by the surgical procedure (range, 35–206 min). For each patient, the mivacurium IR and percent neuromuscular blockade was recorded at the beginning of each 3-min period.

Early in the course of infusion administration, rate adjustments were often necessary to maintain neuromuscular blockade in the desired range (89%–99% blockade). For this reason, an average effective IR that excluded the first 15 min of infusion was calculated for each patient. After the initial 15 min, all patients had at least 15 min of infusion (i.e., five additional 3-min intervals) during which neuromuscular blockade was maintained between 89% and 99%. Data from periods during which neuromuscular blockade was outside this range were not included in the analyses. Within each anesthetic group the average IR for individual patients was averaged to yield a group mean. No weighting based on duration of infusion was used. Mivacurium IRs were calculated on both a $\mu g \cdot kg^{-1} \cdot min^{-1}$ and a $\mu g \cdot m^{-2} \cdot min^{-1}$ basis. The IR of mivacurium required to maintain neuromuscular blockade between 89% and 99% during the first 15 min of infusion was calculated and compared with the IR calculated after the first 15 min of infusion for each patient. A subset of patients in each group that had the longest infusions was also analyzed separately; eight patients in group H received infusions of mivacurium for at least 75 min, and nine patients in group N received infusions of mivacurium for at least 135 min.

Stepwise multiple linear regression was used to assess potential interactions between IR, age, pseudocholinesterase activity, and anesthetic background. Correlation coefficients were calculated to demonstrate associations between independent variables (i.e., age, pseudocholinesterase activity, recovery index) and IR. Paired *t*-test and repeated measures analysis of variance were used to assess changes in infusion requirement with time. *T*-test was used to assess differences in demographic characteristics between groups H and N. Standard errors are shown for all mean values. Statistical differences were considered significant when $P \leq 0.05$.

Results

There were statistically significant differences between groups H and N in age, weight, height, and body surface area: group H, 76.6 ± 6.0 mo, group N, 60.9 ± 4.3 mo; group H, 23.1 ± 1.6 kg, group N, 19.1 ± 0.1 kg; group H, 117 ± 3 cm, group N, 108 ± 3 cm; group H, 0.88 ± 0.04 m^2, group N, 0.77 ± 0.03 m^2 (mean ± SEM).

Table 1. Stepwise Multiple Linear Regression Analysis

Equation (1):		
IR ($\mu g \cdot kg^{-1} \cdot min^{-1}$) =	2.1 pseudocholinesterase (U/L)	[$P = 0.008$]
	−5.6 (10^{-2}) age (mo)	[$P = 0.019$]
	+2.1 anesthetic	[$P = 0.108$]
	+5.7	[$R = 0.51$, $P = 0.001$].
Equation (2):		
IR ($\mu g \cdot m^{-2} \cdot min^{-1}$) =	47 pseudocholinesterase (U/L)	[$P = 0.012$]
	+55 anesthetic	[$P = 0.073$]
	+69	[$R = 0.40$, $P = 0.007$].

IR, infusion rate.

N = 59. For group H, anesthetic = 0; for group N, anesthetic = 1.

Note that anesthetic background does not reach statistical significance in Equations (1) and (2). Removing anesthetic from the equations produces the following:

Equation(3):		
IR ($\mu g \cdot kg^{-1} \cdot min^{-1}$) =	2.1 pseudocholinesterase (U/L)	[$P = 0.006$]
	−6.5 (10^{-2}) age (mo)	[$P = 0.006$]
	+7.2	[$R = 0.48$, $P = 0.001$].
Equation(4):		
IR ($\mu g \cdot m^{-2} \cdot min^{-1}$) =	49 pseudocholinesterase (U/L)	[$P = 0.010$]
	+94	[$R = 0.33$, $P = 0.010$].

When stepwise multiple linear regression analysis was used to assess the effects of pseudocholinesterase activity, patient age, and anesthetic background on IR, pseudocholinesterase had a statistically significant effect on IR (Table 1). There was a significant positive correlation between pseudocholinesterase activity and IR (Table 2). There were no interactions between any of the independent variables in the regression analysis.

Fifty-nine of the 62 patients studied had both pseudocholinesterase activities and dibucaine numbers in the normal range. Two patients from group H had pseudocholinesterase activities more than 20% above normal, and one patient in group N had a dibucaine number more than 20% below normal (Table 3). These three patients were excluded from group analyses (Tables 1–5). The one patient with apparent heterozygous dibucaine resistance and normal pseudocholinesterase activity had a similar response to mivacurium infusion as did other patients in group N with normal pseudocholinesterase activity and normal dibucaine inhibition. The IR of this patient was 15.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. There was no statistically significant difference in the average pseudocholinesterase activity or dibucaine inhibition between groups H and N.

Table 2. Correlation Coefficients Between Infusion Rate and Independent Variables

	IR ($\mu g \cdot kg^{-1} \cdot min^{-1}$) ($P$)	IR ($\mu g \cdot m^{-2} \cdot min^{-1}$) ($P$)	n
Pseudocholinesterase activity (U/L)	0.33 (0.01)	0.33 (0.01)	59
Age (mo)	−0.34 (0.01)	−0.16[a] (0.23)	59
T_{25-75} (min)	−0.36 (0.03)	−0.32[a] (0.06)	36[b]

IR, infusion rate.

Because multiple linear regression demonstrated that pseudocholinesterase was a more significant determinant of mivacurium IR than was anesthetic background, the two anesthetic backgrounds were combined to assess the correlation between pseudocholinesterase, age, and IR.

[a] Not significantly different from zero. All other correlations were statistically significant. P values (two-tailed) are reported in parentheses below the correlation coefficient.

[b] There were only 36 patients for whom T_{25-75} was available.

Although there was no correlation between pseudocholinesterase and age, age did have a significant independent effect on IR when IR was calculated in $\mu g \cdot kg^{-1} \cdot min^{-1}$. Patient age had no effect on IR of mivacurium calculated in $\mu g \cdot m^{-2} \cdot min^{-1}$ (Tables 1 and 2).

There was no statistically significant difference between the IRs for groups H and N when the infusion requirement was referenced to body surface area (Tables 1 and 4). The average IR, in $\mu g \cdot m^{-2} \cdot min^{-1}$, was approximately 20% greater during narcotic than during halothane anesthesia (Table 4). However, the variability in the IRs ($\delta/\sigma = 0.5$) was such that this difference in mean IR did not reach statistical significance with a one-tailed t-test. When IR in $\mu g \cdot kg^{-1} \cdot min^{-1}$ was the dependent variable, both patient age and pseudocholinesterase activity were more significant descriptors of IR than was anesthetic background (Table 1).

The average infusion rate administered during the first 15 min of the infusion of mivacurium was greater than the IR thereafter (paired t-test, $n = 59$). In the nine patients in group N who received a mivacurium infusion for 135 min or longer, repeated measures analysis of variance confirmed a significant change in the rate of infusion with time ($P < 0.01$) (Figure 1). A similar analysis of group N excluding the first 15 min of infusion administration demonstrated no significant change in rate of infusion with time ($P > 0.6$). In the eight patients in group H who had a mivacurium infusion for 75 min or longer, repeated measures analysis of variance confirmed a significant change in rate of infusion with time with or without the first 15 min of infusion administration included in the calculations ($P < 0.01$) (Figure 2). The slight decrease in rate of infusion of mivacurium in the second hour in group H was so small, however, that it was not statistically significant by multiple range tests (Student–Newman–Keuls).

There was no difference in rate of recovery of neuromuscular function between anesthetic groups in terms of 25%–75% recovery index (T_{25-75}) or time to recovery of the train-of-four ratio to ≥0.75 (Table 5). After termination of the infusion, spontaneous recovery from 89%–99% blockade to a train-of-four ratio of ≥0.75 occurred in 9.8 ± 0.4 min ($n = 34$). The T_{25-75} after discontinuation of the infusion was 4.0 ± 0.2 min ($n = 36$). There was no correlation between duration of infusion and T_{25-75}. There was a significant negative correlation between IR in $\mu g \cdot kg^{-1} \cdot min^{-1}$ and T_{25-75} (Table 2). Neostigmine (0.04–0.06 mg/kg) was administered to 22 patients at levels of spontaneous recovery ranging from 10% to 50% (90%–50% blockade). Recovery to a train-of-four ratio of ≥0.75 occurred within 1.2–3.8 min after administration of neostigmine in these 22 patients.

Discussion

In this pediatric study pseudocholinesterase activity was the major factor that influenced the IR for mivacurium. Patients with pseudocholinesterase activity above normal were resistant to the neuromuscular effects of mivacurium administered by infusion. Although one might expect a homozygous dibucaine-resistant patient to be very sensitive to mivacurium, the one child with low dibucaine inhibition in this study responded to an infusion of mivacurium as did children with normal pseudocholinesterase activity and dibucaine inhibition. It would appear that at the relatively low concentrations of mivacurium present in the plasma during an infusion titrated to 95% neuromuscular blockade, and at the even lower concentrations present during recovery from mivacurium, there was sufficient normal pseudocholinesterase in the blood of a presumably heterozygous child to metabolize mivacurium at a normal rate.

Age was found to be an important factor in determining mivacurium IR when IR was calculated on the basis of body weight, but not for IR calculated on the basis of body surface area. There was a small but statistically significant difference between groups H and N with respect to age. The patients in group N were on average 16 mo younger than those in group H. This small but significant difference in age, and hence in body weight/surface area as well, increases the difference between the IRs in $\mu g \cdot kg^{-1} \cdot min^{-1}$ of the anesthetic groups. The average IRs of groups H

Table 3. Effect of Abnormal Pseudocholinesterase Activity or Dibucaine Number on Infusion Rate

Patient	Pseudocholinesterase activity (U/L)	Dibucaine inhibition (%)	Anesthetic group	IR ($\mu g \cdot m^{-2} \cdot min^{-1}$)	T_{25-75}
1	5.2	60	N	474	NA
2	8.5	87	H	588[a]	3.2
3	10.6	73	H	936[a]	3.6

IR, infusion rate; NA, not available.
Normal range: pseudocholinesterase activity = 2.5–7.1 U/L, dibucaine inhibition = 70%–95%.
[a] These two IRs are more than two standard deviations above the mean IR of group H.

Table 4. Mivacurium Infusion Requirements

Group	*n*	IR ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	IR ($\mu g \cdot m^{-2} \cdot min^{-1}$)
H	21	12.4 ± 1.0[a] (4.7–21.8)	315 ± 26 (124–552)
N	38	15.6 ± 0.8[a] (7.8–31.4)	375 ± 19 (197–669)

IR, infusion rate.
Values are mean ± SEM (range).
[a] $P < 0.05$, statistically significant difference between anesthetic groups.

Table 5. Spontaneous Recovery After Termination of Mivacurium Infusion

Group	T_{25-75}	T4/T1 ≥ 0.75
H	3.8 ± 0.3 ($n = 15$)	10.3 ± 0.8 ($n = 14$)
N	4.1 ± 0.3 ($n = 21$)	9.4 ± 0.4 ($n = 20$)

There was no statistically significant difference between anesthetic groups.
Values are mean ± SEM.

and N differed by about 30% when calculated on the basis of weight and by only 20% when calculated on the basis of body surface area.

The fact that age was *not* significant in determining mivacurium IR based on body surface area, but *was* an important factor in determining mivacurium IR based on body weight, suggests that the influence of age on IR is related to developmental changes in extracellular fluid volume. The infusion rate would be expected to depend on the sensitivity of the neuromuscular junction to the drug and on the clearance of the drug (13). Beyond the age of 2 yr, significant change in the sensitivity of the neuromuscular junction to nondepolarizing neuromuscular blocking agents is unlikely (14,15). Nevertheless, a change in the volume of distribution of a neuromuscular blocking drug may well occur in patients between 2 yr of age and adulthood. The volume of distribution may be expected to decrease with increasing age and decreasing volume of extracellular fluid per kilogram body weight. However, the ratio of extracellular fluid volume to body surface area is relatively unchanged with age. For mivacurium there was a significant difference in the ED_{50}, calculated in μg/kg, between children and adults during nitrous oxide-narcotic anesthesia (1). When the ED_{50} was calculated on the basis of body surface area, there was no significant age-related difference (1). These observations suggest that there are age-related changes in the volume of distribution of mivacurium, but not in the effective plasma concentrations. If the effective plasma concentrations do not change with age, then the age-related changes in IR ($\mu g \cdot kg^{-1} \cdot min^{-1}$) must be related to changes in clearance of mivacurium that parallel the expected age-related changes in volume of distribution. Referencing IR to body surface area rather than to weight appears to control for such age-related changes in this study, because age is not a significant factor influencing mivacurium IR ($\mu g \cdot m^{-2} \cdot min^{-1}$). There appear to be similar age-related changes in the clearance and volume of distribution of atracurium (16). In contrast, the clearance of many other neuromuscular blocking drugs, those that are not removed from the blood predominantly by processes occurring in the plasma, does not increase proportionately with the volume of distribution (14,17).

In children, referencing mivacurium IR to body surface area rather than to weight eliminated age as an important predictor of IR. However, differences in IR are present between pediatric and adult patients whether IR is calculated on the basis of body weight or body surface area. The mivacurium IR in adults during nitrous oxide-narcotic anesthesia is about 250 $\mu g \cdot m^{-2} \cdot min^{-1}$ (6.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or less (11,12), whereas in children in this study receiving a similar anesthetic, mivacurium IR is 375 $\mu g \cdot m^{-2} \cdot min^{-1}$ (15.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$). It is expected that the infusion requirement at steady state will be determined by required plasma concentration and clearance (13). The disparity between children and adults in mivacurium IR based on $\mu g \cdot m^{-2} \cdot min^{-1}$ suggests that

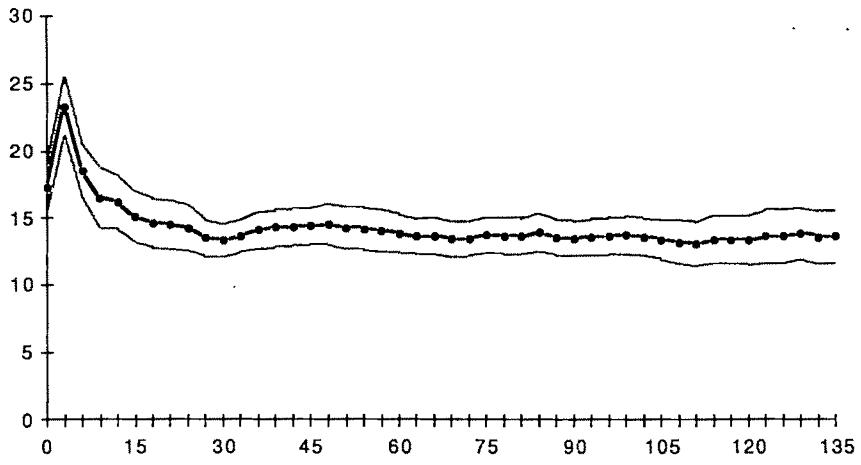

Figure 1. x-axis, time in minutes; y-axis, infusion rate is rate (μg·kg^{-1}·min^{-1}) required to maintain 89%–99% neuromuscular blockade (mean ± SEM). Rate of mivacurium infusion at 3-min intervals from the start of infusion through the first 135 min in the nine patients in group N with the longest duration of infusion.

there may be significant age-related differences in the clearance of mivacurium that are independent of the change in weight/surface area ratio with age. There may be significant changes in pseudocholinesterase activity with age that could not be identified in these studies. Pharmacokinetic studies of mivacurium may provide direct answers to questions regarding the clearance of mivacurium. At present one could only estimate the mean residence time of mivacurium from the ratio of ED_{95} and IR titrated to produce 95% neuromuscular blockade (18). From these data in children (2717 μg·m^{-2}/423 μg·m^{-2}·min^{-1}) the mean residence time of mivacurium is about 6 min. Similar data in adults (3067 μg·m^{-2}/290 μg·m^{-2}·min^{-1}) (1,11,12) suggest that the mean residence time of mivacurium in adults is close to 10 min.

Previous studies of the effects of halothane on potentiation of neuromuscular blockade in children have reported somewhat conflicting results. In a study of atracurium infusion requirements that employed stimulus parameters identical to those of this study of mivacurium infusion requirements and similar electromyographic monitoring of neuromuscular function (19), halothane (0.8% end-tidal) significantly potentiated atracurium-induced neuromuscular blockade by about 30%. In a study administering a single stimulus at 0.1 Hz (rather than a train-of-four stimuli) and force transduction monitoring (20), there was no significant potentiation by halothane of neuromuscular blockade produced by infusion of atracurium. The study of the mivacurium dose-response relationship with methods identical to those of this infusion study (1) demonstrated a significant potentiation of 15%–20% by halothane (0.8% end-tidal). A mivacurium dose-response study with similar stimulation parameters, but with force transduction monitoring (2), failed to demonstrate potentiation by halothane. Neither of these studies of mivacurium (1,2) found a significant delay in the rate of spontaneous recovery of neuromuscular function during

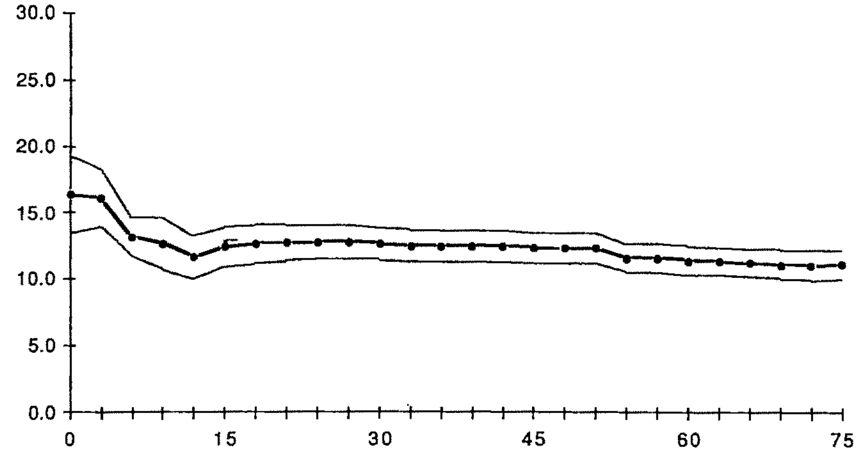

Figure 2. x-axis, time in minutes; y-axis, infusion rate is rate (μg·kg^{-1}·min^{-1}) required to maintain 89%–99% neuromuscular blockade (mean ± SEM). Rate of mivacurium infusion at 3-min intervals from the start of infusion through the first 75 min in the eight patients in group H with the longest duration of infusion.

halothane anesthesia. It would appear that potentiation of mivacurium-induced neuromuscular blockade by halothane may be less than potentiation of atracurium-induced neuromuscular blockade. In any case, the interpatient variability in mivacurium infusion requirement was too large to allow observation of a statistically significant potentiation by halothane in the present study.

In conclusion, mivacurium can be administered to children during either nitrous oxide-halothane or nitrous oxide-narcotic anesthesia for several hours with no evidence of cumulation and with rapid spontaneous or pharmacologically induced return of neuromuscular function after termination of infusion. The average IR calculated here would be useful as an initial IR. However, as interpatient variability is more than threefold, infusions should be titrated to effect, as documented by appropriate neuromuscular monitoring.

We thank Wayne DellaMaestra for his valuable assistance with data analysis, and Lillian Hankins, without whom the study could not have progressed as scheduled.

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The Antinociceptive Role of μ- and δ-Opiate Receptors and Their Interactions in the Spinal Dorsal Horn of Cats

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OMOTE K, KITAHATA LM, COLLINS JG, NAKATANI K, NAKAGAWA I. The antinociceptive role of μ- and δ-opiate receptors and their interactions in the spinal dorsal horn of cats. Anesth Analg 1990;71:23–8.

This study was undertaken to examine the antinociceptive roles of different subtypes of opiate receptors and their interactions at the level of the spinal cord. We recorded extracellularly the activity of the single wide dynamic range neurons evoked by noxious radiant heat (51°C) in decerebrate, spinally transected cats. The separate intrathecal administration of DAGO (selective μ-agonist, $n = 28$), morphine (less selective μ-agonist, $n = 22$), DPDPE (selective δ-agonist, $n = 25$), and DADL (less selective δ-agonist, $n = 17$) produced statistically significant suppression of noxiously evoked activity in a time- and dose-dependent manner. In addition, intravenously administered naloxone (nonselective opiate antagonist) reversed the suppressive effects of all opiates studied. Intravenously administered ICI 174,864 (selective δ-antagonist) reversed the effects of DPDPE. These results, based on relative selectivity for opiate receptors, indicate that both μ- and δ-opiate receptors can modulate the input of nociceptive information in the spinal dorsal horn. To study interactions between μ- and δ-receptors at the level of the spinal cord, a combination of the above agonists was injected intrathecally—namely, an ineffective or slightly effective dose of DAGO (1 or 1.5 μg, respectively) that was combined with an ineffective dose of DPDPE (30 μg). The intrathecal combination of DAGO and DPDPE produced significant synergistic suppressive effects of noxiously evoked activity. These findings, again based on relative selectivity, suggest that drug combinations that include both selective μ- and δ-agonists may be a useful method of lowering the total amount of any one drug, thus decreasing the likelihood of side effects, while at the same time producing significant analgesia. Clearly, combinations of other μ- and δ-agonists should be studied to confirm the utility of such combinations.

Key Words: ANALGESICS, RECEPTORS—spinal cord. RECEPTORS, OPIATES—μ, δ. SPINAL CORD, OPIATE RECEPTORS.

Spinal analgesia utilizing opiate agonists is the result of specific agonist-opiate receptor interactions in the spinal cord. Clinical application of spinal opiates has proven to be an important means of controlling acute and chronic pain in humans.

Martin et al. (1) suggested three opiate receptor subtypes (μ, κ, and σ) in the chronically spinalized dog preparation. Lord et al. (2) postulated the presence of a distinct receptor selective for the enkephalins that was termed the δ-receptor. Thereafter, binding assays confirmed the existence of μ-, δ-, and κ-receptors (3–5). The status of the σ-receptor is unclear, but it is unlikely that it is involved in analgesia. Initial opinion was that analgesia was mediated by μ-receptors but not δ-receptors in the central nervous system (6–8). However, considerable evidence for δ-receptor-mediated analgesia, particularly at the spinal level, has been accumulating (9–13). The development of highly selective opiate agonists has been needed to substantiate the specific opiate subtypes involved in spinal opiate analgesia. A great deal of effort to develop highly selective agents has produced [D-Ala^2, MePhe^4, Gly^5-ol] enkephalin (DAGO), and [D-Pen^2, D-Pen^5] enkephalin (DPDPE), which have been found to exhibit a high degree of selectivity for μ- and δ-receptors, respectively (14,15).

One of the purposes of this study was to compare the ability of intrathecally administered opiate prototypes (selective μ-agonist DAGO, less selective μ-agonist morphine sulfate [MS], selective δ-agonist

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DPDPE, less selective δ-agonist [D-Ala^2-D-Leu^5] enkephalin [DADL]) to suppress noxiously evoked activity of wide dynamic range (WDR) neurons in the spinal dorsal horn of decerebrate, spinal cats. Furthermore, the relative selectivity of these agents was evaluated by comparing the reversibility of neuronal suppression by the nonselective opiate antagonist naloxone with that produced by the selective δ-antagonist, *N,N*-diallyl-Tyr-Aib-Phe-Leu-OH (ICI 174,864) (16).

The other purpose of this investigation was to examine the potential synergistic effects of the selective agonists. The complicated pharmacology associated with modulation of sensory information at the level of the spinal cord provides an opportunity for the development of more effective ways to block the processing of pain information. We are interested in determining if there is an interaction between selective μ- and δ-opiate agonists at the spinal level. If the combination of μ- and δ-receptor agonists at doses that alone produce no or only minimal effects shows significant suppression of noxiously evoked activity of WDR neurons, then the clinical use of such combinations may help to avoid complications including respiratory depression, physical dependency, and/or tolerance.

Methods

The protocol of this study was approved by the Yale Animal Care and Use Committee, and institutional, state, and federal guidelines for the humane care and use of laboratory animals were observed during all aspects of this study. Details of the experimental methods have been previously described (17). Ninety-six cats of both sexes, weighing between 3 and 4.2 kg, were prepared for electrophysiologic experiments. General anesthesia (halothane, nitrous oxide, and oxygen) was used for the surgical preparation, which included tracheostomy and catheterization of a jugular vein and a carotid artery. Animals were rendered decerebrate by bilateral electrolytic lesions in the midbrain reticular formation. Decerebration rendered the animals unconscious and enabled general anesthesia to be discontinued. A laminectomy was performed from L-4 to L-6, exposing the lumbar spinal cord. The dura was cut and reflected and physiologic saline at 37°C bathed the spinal cord. The lungs were mechanically ventilated with 100% oxygen and physiologic variables (blood pressure, body temperature, and end-tidal CO_2) were monitored and maintained within normal limits.

For each experiment, a tungsten microelectrode was inserted by hydraulic micromanipulator into the lumbar enlargement of the spinal dorsal horn. While the electrode was advanced into the spinal cord, the receptive fields on the ipsilateral hind leg were stimulated. After isolation of a single neuron, the neuron type was identified by the characteristic response to the following stimuli: air puff, light touch with a camel hair brush, pinch with forceps, cooling with ethyl chloride spray, and noxious radiant heat (51°C). A neuron was classified as a WDR neuron based on its response profile to increasing intensities of receptive field stimulation. After identification of a WDR neuron, as a control study, noxious radiant heat (51°C, 8 s) was focused on the center of the receptive field, and the noxiously evoked activity of the neuron was recorded. A thermocouple, which provided feedback for stimulus control, was positioned adjacent to the center of the receptive field to maintain the stimulus temperature constant.

After control studies, the physiologic saline that had been bathing the spinal cord was carefully removed and gently replaced with 0.5 mL of drug-saline solution. The drugs used in the experiment were DAGO and DPDPE (Peninsula Laboratories, Belmont, Calif.), DADL and ICI 174,864 (Cambridge Research Biochemicals, Valley Stream, N.Y.), morphine sulfate (Mallinckrodt, St. Louis, Mo.), and naloxone hydrochloride (Manati, Puerto Rico). Intrathecally administered agonists consisted of 1, 1.5, 10, and 20 μg of DAGO (n = 6, 6, 10, and 6, respectively) or 25, 200, and 400 μg of MS (n = 8, 7, and 7, respectively), 20, 100, and 250 μg of DADL (n = 6, 5, and 6, respectively), or 30, 100, and 200 μg of DPDPE (n = 6, 6, and 13, respectively). Subsequent to spinal agonist administration, noxiously evoked activity of the individual WDR neurons by radiant heat was recorded every 3 min for periods up to 30 min. In most experiments, the ability of naloxone or ICI 174,864 to reverse the effects of agonists was examined by administering 100 μg of naloxone or 200 μg of ICI 174,864 intravenously 31 min after agonist administration.

In combination studies, in order to examine the interaction between DAGO and DPDPE, an ineffective or slightly effective dose (1 or 1.5 μg, respectively) of DAGO was combined with an ineffective dose of DPDPE (30 μg). After the control study, the combination of 1 μg (n = 6) or 1.5 μg (n = 6) of DAGO and 30 μg of DPDPE was gently applied to the spinal cord. Naloxone (100 μg) was intravenously administered at 31 min after the application of the combined agonists.

All data were collected on line and analyzed on line as well as off line by a PDP 11/40 computer. The

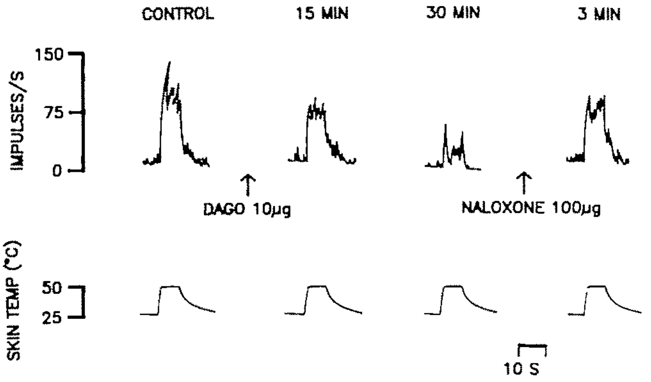

Figure 1. Effects of DAGO on a single WDR neuron. Intrathecal DAGO (10 μg) suppressed the evoked activity to 23% of control at 30 min and intravenous naloxone (100 μg) produced reversal to 81% of control.

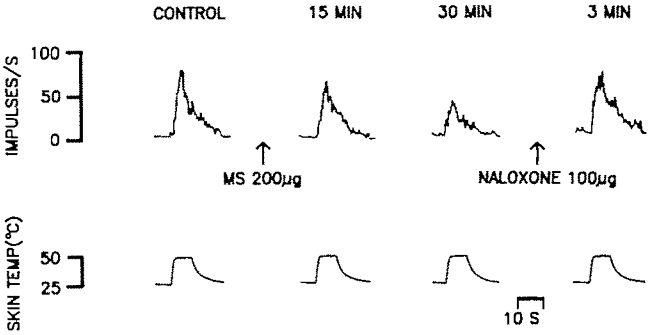

Figure 2. Morphine effects on a single WDR neuron. Intrathecal MS (200 μg) suppressed activity to 47% of control at 30 min and naloxone (100 μg) reversed to 118% of control.

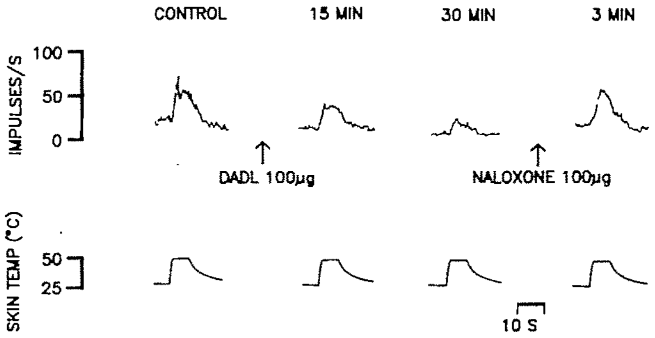

Figure 3. Effects of DADL on a single WDR neuron. Intrathecal DADL (100 μg) suppressed activity to 36% of control at 30 min and naloxone (100 μg) reversed to 83% of control.

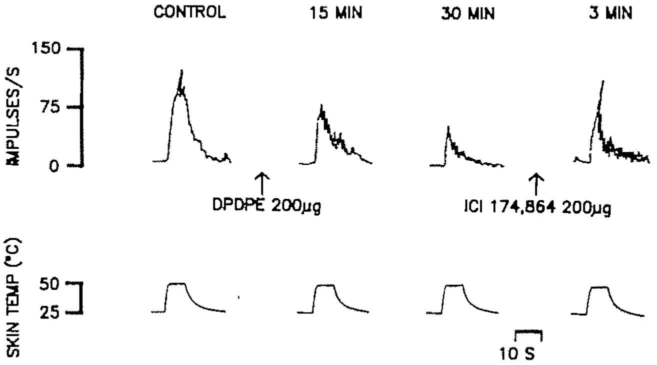

Figure 4. Effects of DPDPE on a single WDR neuron. Intrathecal DPDPE (200 μg) suppressed to 32% of control at 30 min and intravenous ICI 174,864 (200 μg) reversed to 66% of control.

integrated neuronal activity and the analog skin temperature were recorded on a polygraph. The variables were expressed as percent of control values or as percent suppression, plus or minus standard error of the mean. The dose-dependent suppression of opiates was analyzed using analysis of variance followed by Student's *t*-test. The reversal effects of antagonists and the suppressive effects of combined agonists were analyzed using paired and unpaired Student's *t*-test, respectively. A two-tailed P value of <0.05 was considered to be statistically significant.

Results

Data were obtained from 96 neurons. All neurons from which noxiously evoked activity was recorded were classified as WDR neurons. The neurons were recorded at a depth of 1798 ± 687 μm (mean ± SD) below the surface of the spinal cord. In two neurons, after isolation, drug-free physiologic saline instead of opiates was applied to the spinal cord. Neither sensitization nor fatiguing of the response occurred within 30 min. Drug-free physiologic saline was found to have no effect on the noxiously evoked activity of WDR neurons.

Antinociceptive Effects of μ- and δ-Agonists

Figures 1–4 show the effects of 10 μg of intrathecally administered DAGO (Figure 1), 200 μg of MS (Figure 2), 100 μg of DADL (Figure 3), and 200 μg of DPDPE (Figure 4) on the neuronal activity of individual WDR neurons. Intrathecally administered opiates that possess μ, δ, or both activities suppressed the evoked activity of WDR neurons studied. The dose-response regression lines for intrathecally administered DAGO, MS, DADL, and DPDPE 30 min after drug administration are shown in Figure 5. The dose-response relationship for each of the opiates used in this study demonstrated good linear correlation and the rank order of potency was found to be DAGO > DADL > MS = DPDPE.

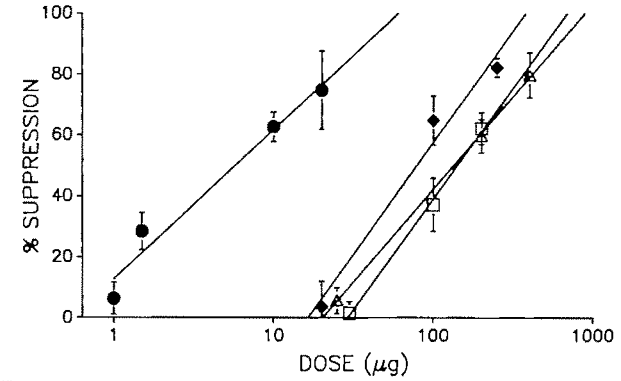

Figure 5. The dose-response regression lines for DAGO (*filled circles*), MS (*open triangles*), DADL (*filled diamonds*), and DPDPE (*open squares*). The regression lines represent the percent suppression seen 30 min after intrathecal administration of opiate agonists. DAGO ($r = 0.985$, $P < 0.01$), MS ($r = 0.999$, $P < 0.01$), DADL ($r = 0.988$, $P < 0.01$), and DPDPE ($r = 0.998$, $P < 0.01$).

Effects of Antagonists

The effect of intravenous naloxone ($n = 4$) or ICI 174,864 ($n = 4$) alone on the evoked neuronal activity was examined. Antagonists alone produced neither excitation nor suppression of WDR neuronal activity.

Examples of the reversal effects of 100 μg of intravenously administered naloxone (Figures 1–3) or 200 μg of ICI 174,864 (Figure 4) are shown at the right side of the figures. One hundred micrograms of naloxone reversed the effects of DAGO (23%–81% of control), MS (47%–118% of control), and DADL (36%–83% of control). The effects of DPDPE were reversed by 200 μg of ICI 174,864 (32%–66% of control). The effects of intravenous naloxone and ICI 174,864 on the suppression of the mean evoked activity of the WDR neurons in this study are shown in Figure 6. Naloxone produced a reversal of all agonist-induced suppression (upper plot in Figure 6); in contrast, ICI 174,864 reversed only the effects of DPDPE (lower plot in Figure 6).

Interaction Between DAGO and DPDPE

As we see in Figure 5, 1 μg of DAGO and 30 μg of DPDPE were ineffective in suppressing noxiously evoked activity. The 1.5-μg dose of DAGO produced approximately 29% suppression. Figure 7 demonstrates that in a single cell 1 μg of intrathecally administered DAGO or 30 μg of DPDPE produced no suppressive effect on noxiously evoked activity. In contrast to the ineffectiveness of 1 μg of DAGO or 30 μg of DPDPE alone, the combination of 1 μg of DAGO and 30 μg of DPDPE produced a significant suppression of noxiously evoked activity (Figure 8).

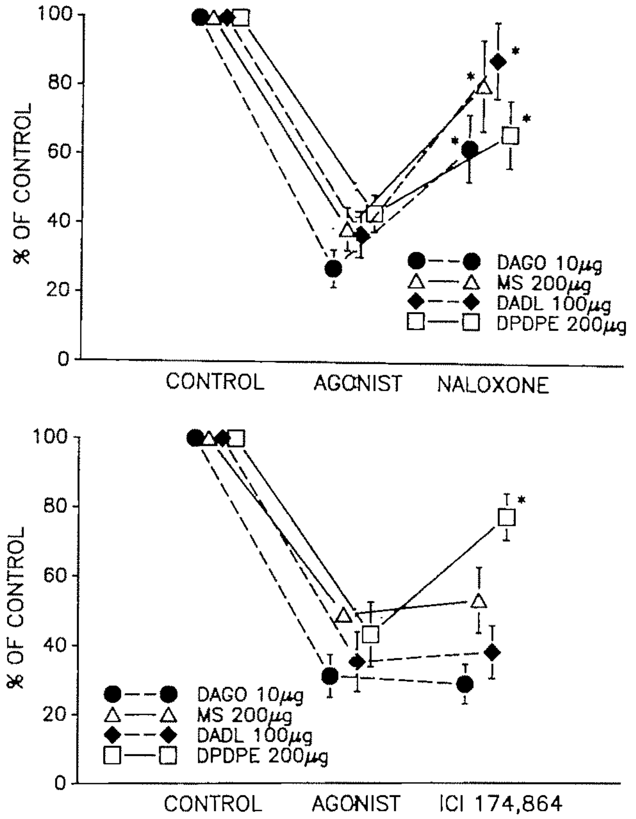

Figure 6. Reversal effects of 100 μg intravenous naloxone (*top*) and 200 μg intravenous ICI 174,864 (*bottom*) on the WDR neuronal suppression of DAGO (10 μg), MS (200 μg), DADL (100 μg), and DPDPE (200 μg) administered intrathecally. Data represent the values at 30 min after opiate agonist administration and 3 min after intravenously administered naloxone or ICI 174,864. *$P < 0.05$ compared with the values at 30 min after opiate administration.

This effect was reversed by 100 μg of intravenous naloxone to 94% of control value (Figure 8). Results of the combination studies are summarized in Figure 9. Although ineffective doses of DAGO (1 μg) or DPDPE (30 μg) alone produced no significant suppression of the noxiously evoked activity, the combination of these two ineffective doses produced a significant synergistic effect (25% suppression). When the dose of DAGO was increased to 1.5 μg, it was capable of producing 29% suppression. When this was combined with an ineffective dose of DPDPE (30 μg), the combined drugs produced synergistic suppression (55% suppression) of noxiously evoked activity.

Discussion

Using a sensitive neurophysiologic assay, the present study has demonstrated that the intrathecal administration of DAGO, MS, DADL, or DPDPE is capable of

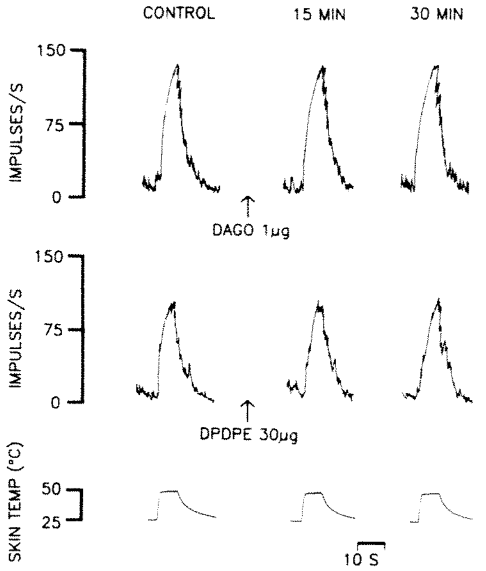

Figure 7. Lack of effect of 1 μg of DAGO or 30 μg of DPDPE administered intrathecally on the noxiously evoked activity of single WDR neurons. Intrathecal administration of 1 μg of DAGO or 30 μg of DPDPE produced no suppression of the activity for a period of up to 30 min.

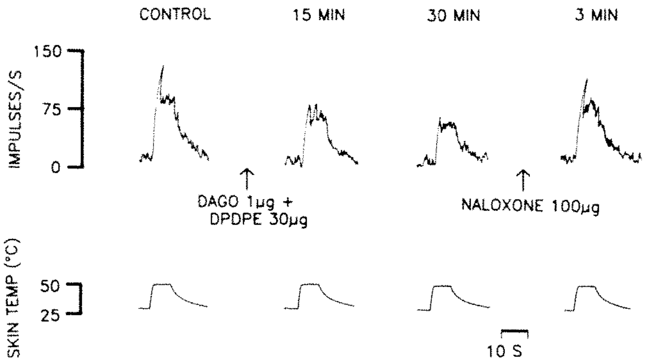

Figure 8. Effect of the combination of 1 μg DAGO and 30 μg DPDPE on the evoked activity of a single WDR neuron. This combination suppressed the evoked activity to 65% of control value at 30 min. Intravenously administered naloxone (100 μg) reversed the suppressive effect to 94% of control value.

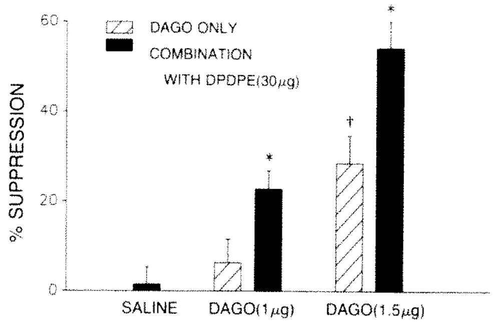

Figure 9. Interaction of DAGO and DPDPE. Data are presented as the percent suppression at 30 min after intrathecal opiates. One microgram of DAGO ($n = 6$) or 30 μg of DPDPE ($n = 6$) produced no significant suppression of the mean evoked activity. DAGO (1.5 μg) ($n = 6$) produced slight neuronal suppression. One microgram or 1.5 μg of DAGO combined with 30 μg of DPDPE ($n = 6$ or 6, respectively) produced synergistic suppression of noxiously evoked activity. *$P < 0.05$ compared with the suppression values of DAGO only. †$P < 0.05$ compared with control values.

suppressing noxiously evoked activity of spinal WDR neurons in a dose-dependent manner in decerebrate, spinal-cord-transected cats. The relative selectivity of these agonists as well as the selective reversal by the δ-antagonist ICI 174,864 reaffirms the importance of both μ- and δ-receptors in this process. Wide dynamic range neurons have been identified as cells of origin for the spinothalamic tract and are likely to be associated with the transmission of noxious information. This indicates that opiate agonists with affinity for μ- or δ-opiate receptors are likely to modify the spinal transmission of information about noxious input. The nonselective antagonist naloxone has reversed the effects of all opiates studied, and, in contrast, the selective δ-agonist ICI 174,864 has reversed only the effects of DPDPE. ICI 174,864 reversal thus indicates that the neuronal suppression of DPDPE is due to interaction of the δ-agonist with the δ-opiate receptor. One of the important results of the present study is that a significant suppressive effect of the evoked activity of WDR neurons is generated by a combination of the selective μ-agonist and the selective δ-agonist at doses that by themselves produce only minimal effects. These results provide neurophysiologic evidence that there is an important interaction at the spinal level between μ- and δ-agonists. A clinical consequence of this would be the ability to produce an adequate physiologic effect with a minimum degree of activation of the respective receptors. Rothman and Westfall (18,19) have obtained evidence of noncompetitive interactions between μ- and δ-ligands, using a binding assay in rat brain, and proposed that distinct μ- and δ-receptors coexist in an opiate-receptor complex. Thus, it has been demonstrated that δ-opiate agonists are capable of enhancing the antinociceptive potency of morphine at the supraspinal level (20,21). At the spinal level, the question of such interactions is controversial (22,23). The results of the present study, using an electrophysiologic method, support the work of Larson et al. (22), who demonstrated that subeffective doses of intrathecal leu-enkephalin (δ-preferring agonist) reduced the analgesic ED_{50} of intrathecal morphine in a behavioral analgesic model. The coadministration of other μ- and δ-agonists will help to define better the utility of such combinations.

Analgesics thought to act at the μ-receptor are believed to be associated with serious side effects, including respiratory depression and physiologic dependence. Spinal antinociception through δ-receptors may provide analgesia with diminished adverse effects as it is suggested that δ-mediated analgesia is less associated with respiratory depression (24,25), physical dependence (26,27), and tolerance (27). The complex pharmacology of the spinal cord offers good possibilities for rational advances in pain management. Several lines of evidence demonstrated that no cross-tolerance or slight cross-tolerance between μ- and δ-agonists at the spinal level was observed in animals (9,10,28) or humans (25,29). The multidrug combination of selective μ- and δ-opiate agonists may allow a significant reduction in the use of any single agonist, thereby decreasing or eliminating the serious side effects of opiate administration.

The future of intrathecally or epidurally administered opiates for pain management may be enhanced by the use of highly selective opiate subtype agonists in a multidrug combination to reduce the occurrence of possible complications. Although the drugs employed in this study are unlikely to have a significant effect on κ-receptors, κ-receptor interactions are likely to add to the analgesic effectiveness of a multidrug combination.

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Decrease in Vascular Resistance in the Isolated Canine Hindlimb After Graded Doses of Alfentanil, Fentanyl, and Sufentanil

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WHITE DA, REITAN JA, KIEN ND, THORUP SJ. Decrease in vascular resistance in the isolated canine hindlimb after graded doses of alfentanil, fentanyl, and sufentanil. Anesth Analg 1990;71:29–34.

Under halothane anesthesia five dogs were prepared with both hindlimbs isolated from the systemic circulation to allow intermittent placement on extracorporeal perfusion at constant flow. One limb of each dog was surgically denervated. In this relatively anesthetic-free preparation, graded equivalent doses of alfentanil, fentanyl, and sufentanil were infused over 30 s, and vascular resistance was measured. Increasing opioid administration caused a progressive diminution in peripheral resistance. By the high dose level, alfentanil (500 μg/kg), fentanyl (50 μg/kg), and sufentanil (6 μg/kg) caused equal and significant decreases of 48%, 48%, and 44% in resistance, respectively. There was no difference among the opioids in effects on resistance at equivalent dosages. Neither pretreatment with naloxone nor denervation changed the response to the narcotics. We conclude that the three synthetic opioids produce vasodilation by direct action on the peripheral vascular smooth muscle.

Key Words: ANALGESICS—fentanyl, sufentanil, alfentanil. ARTERIES, VASODILATION—fentanyl, sufentanil, alfentanil.

The short-acting, potent synthetic narcotics are used with increasing frequency for surgery in people with significant coronary artery disease. Initially, fentanyl was said to cause little perturbation in myocardial function and vascular tone in clinical studies (1) and to cause only a small decrease in blood pressure under controlled circumstances of animal investigation (2). However, as larger doses were administered and more extensive clinical experience was obtained, systemic vascular resistance was found to decrease in the clinical situation (3).

The later generation synthetic opioids, especially sufentanil, have been shown to cause moderate peripheral vascular dilation in humans, although their relative cardiovascular depression has been postulated to be either less (4) or greater (5,6) than that of fentanyl.

Although some of the decrease in blood pressure observed after the administration of synthetic opioids may be due to direct myocardial depression or a lessening of venous return, a substantial part is probably the result of vasodilation in the peripheral arterial tree. The purpose of our study was to compare the peripheral vascular effects of alfentanil, fentanyl, and sufentanil at equipotent doses in an isolated canine hindlimb without significant anesthesia interaction and independent of neuronal reflex.

Methods

Under halothane endotracheal anesthesia, both hindlimbs of five mongrel dogs (25–31 kg) were isolated vascularly by placing tourniquets around the thigh at the most cephalad position possible at both sides of the femoral vessels and tightening them with vise clamps (Figure 1). The femoral and sciatic nerves were isolated and kept free of tourniquet compression. The obturator nerve and vascular complex were dissected free when possible. In one limb of each animal, the nerves were severed to facilitate denervation of the limb and, in the other, they were left intact. All proximal side circulation to the main femoral vessels was ligated. Polyvinyl catheters were inserted into both the proximal and distal segments of the femoral artery and vein just below the inguinal ligament in a "Y" configuration that allowed for either extracorporeal limb perfusion or systemic flow through. The femoral vessels were severed in the denervated limb and were left uncut in the inner-

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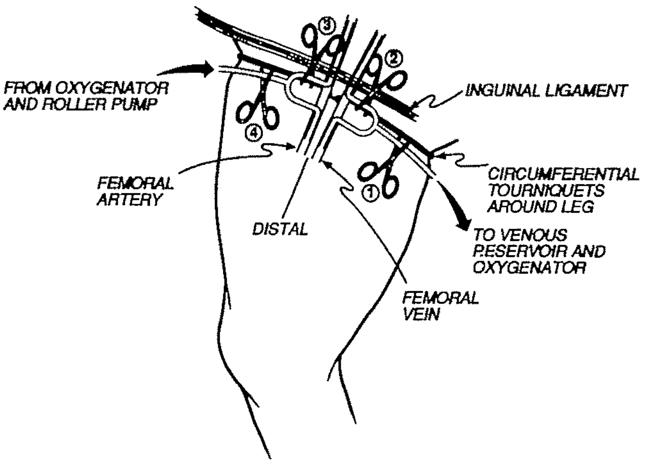
FROM OXYGENATOR AND ROLLER PUMP
③
②
INGUINAL LIGAMENT
④
CIRCUMFERENTIAL TOURNIQUETS AROUND LEG
FEMORAL ARTERY
①
DISTAL
TO VENOUS RESERVOIR AND OXYGENATOR
FEMORAL VEIN

Figure 1. An artist's illustration of the hindlimb model. Tourniquets were placed tightly as cephalad as possible around the muscle bundles of the upper leg. The femoral artery, vein, and nerve, sciatic nerve, and obturator nerve were isolated. The femoral artery and vein were cannulated above the inguinal ligament and distally into the leg. The "Y" arrangement of the cannulas allowed for either systemic or oxygenator blood flow through the leg. See text for details.

vated leg. Blood from the proximal portion of the femoral vein flowed by gravity to the venous reservoir of the bubble-oxygenated infant cardiopulmonary bypass machine (model S070, Shiley Corp., Tustin, Calif.). On the inflow line a "Starling" resistor of 7 cm H_2O pressure was placed to approximate normal venous pressure. Gravity fed blood from the venous reservoir through the membrane oxygenator and therein to a bubble trap and particulate filter. A calibrated roller pump sent the oxygenated blood into the distal femoral artery at a prescribed constant flow rate. The oxygenator was primed with 400 mL of heparinized compatible canine blood and the paws were clamped off by wire tourniquets to obviate the effects of arteriovenous fistulae there.

Catheters were placed in the carotid artery and both cranial tibial arteries for systemic and limb pressure measurements, respectively. A central venous catheter was placed in the external jugular vein, and core temperature was measured in the esophagus. Temperature in the hindlimbs was transduced from needle thermistors placed in large muscle groups. A heating blanket controlled systemic temperature, while heat lamps maintained limb temperature.

Isolation of the hindlimb circulation was obtained by closing clamps 2 and 3 to shut off systemic flow and opening clamps 1 and 4 perfusing through the oxygenator (Figure 1). The 95% O_2–5% CO_2 gas flow over the membrane was adjusted to keep acid-base values normal and provide a rapid washout of halothane from the limb. The roller pump speed was set to produce an arterial pressure of approximately 65 mm Hg after washout and the flow setting was kept constant thereafter. With an unvaried flow, arterial pressure reflected vascular resistance directly by the formula

$$\text{Resistance} = (\text{Arterial pressure} - 5\ \text{mm Hg})/\text{Flow rate}.$$

After a halothane washout period of 35 min, graded doses, based on limb weight, of either alfentanil, fentanyl, or sufentanil were infused over 30 s into the arterial cannula of the bypass unit. A relative potency of 1:10:80 in the dog was used for alfentanil, fentanyl, and sufentanil, respectively (Janssen brochure, 1981). Limb weight was assumed as 10% of body weight, and the 400-mL reservoir prime volume was added for calculation of the amount of drug given. The doses were as follows: alfentanil—50, 300, and 500 μg/kg; fentanyl—5, 30, 50 μg/kg; sufentanil—0.6, 3.6, and 6 μg/kg of limb weight. During the administration of each drug a cumulative dosing schedule was used so that a low, medium, and high dose was injected into the limb sequentially. Pressure measurements and venous blood samples were taken at the point of maximum vascular response (usually within 3 min after drug administration), followed by a 5-min stabilization period before the next incremental dose was given. The drugs were prepared from the citrate or hydrochloride salt dissolved in normal saline; the solutions were made fresh before each study. An infusion of an equal volume of normal saline was given as a sham procedure before the administration of the initial narcotic.

At the end of each individual narcotic protocol, systemic circulation was reestablished for 30 min and the reservoir perfusate emptied several times into the systemic circulation to clear the previous opiate out of the limb by redistribution and systemic metabolism. Thereafter the limb was again placed on bypass and another of the three opioids was studied. A venous blood sample for measurement of the concentration of the previous narcotic was taken at the start of each new narcotic study to determine the efficacy of the systemic clearance of the earlier narcotic(s). The sequence of narcotics studied in each dog was chosen randomly.

Serum concentrations of the three drugs were determined by standard radioimmunoassay using labeled alfentanil, sufentanil, and fentanyl supplied by Janssen Laboratories (Beerse, Belgium [7]). Sensitivity of the test was <1 ng/mL.

In three dogs, 0.5 mg/kg naloxone was perfused into the limb at the end of the three-narcotic study and the high fentanyl dose was repeated (50 μg/kg).

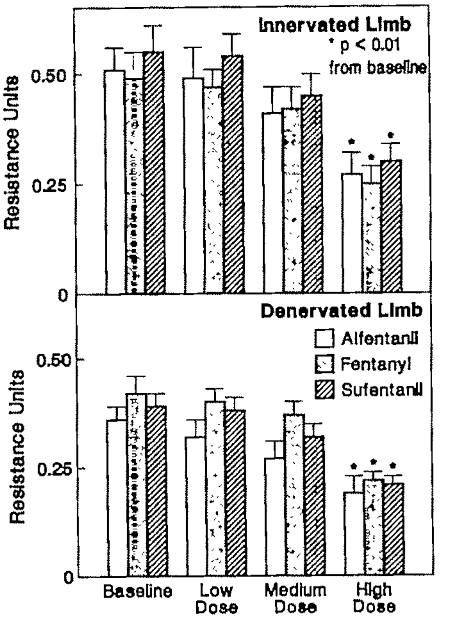

Figure 2. Bar graphs of the resistance units for both the innervated and denervated limbs. All three drugs produced a progressive decrease in vascular resistance from baseline which reached statistical significance by the high dose (*$P < 0.01$), but there was no difference among alfentanil, fentanyl, and sufentanil.

The effects of the antagonist and the narcotic were observed to delineate the role of peripheral opiate receptors in mediating the changes in vascular resistance.

The protocol was approved by the University Animal Care Committee and statistical analysis of the data was performed by analysis of variance and Student's *t*-test. A *P* value of <0.05 was considered statistically significant. All values are expressed as the mean ± SEM unless specified otherwise.

Results

All three narcotics reduced limb vascular resistance progressively in a dose-dependent fashion (Figure 2). There was no difference in the decrease in resistance units among the three drugs at any individual dose in the innervated or denervated preparation and the percent changes from control values were remarkably constant as well. Not until the highest doses of alfentanil, fentanyl, and sufentanil were given were there, however, statistically significant decreases in vascular resistance of 48.0%, 48.0%, and 44.3%, respectively, in the innervated limb. Results in the denervated limb were similar: alfentanil, −47.9%; fentanyl, −47.6%; and sufentanil, −47.2%. There was no significant change in resistance caused by the diluent vehicle.

The baseline values for arterial pressure, flow, and the resistance units in the limb are displayed in Table 1. Limb flow stayed constant throughout the experiment. Vascular resistance started off significantly lower and flow significantly greater in the denervated extremity than in the innervated limb before the administration of opioids.

Table 2 gives the venous blood concentrations of the three narcotics at the times of peak effect on vascular resistance. The ratios among the blood levels of the opioids increased as the dosage increased, but averaged approximately 1:4:100 for sufentanil, fentanyl, and alfentanil, respectively. The concentration of previously administered narcotics in the blood before the start of a new narcotic study is shown in the last column in Table 2. Values were approximately one-tenth the low-dose concentration for each drug.

The stability of the preparation is demonstrated in Table 3. Core and limb temperatures were maintained at normal levels. Arterial blood gas tensions were consistent with normal acid-base balance in dogs, and hematocrits remained between 34% and 36%.

When the limb was infused with 0.5 mg/kg of naloxone, vascular resistance decreased 15.5% ± 2.3% and 10.0% ± 1.9% in the innervated and denervated limbs, respectively. However, injection of 50 μg/kg of fentanyl into the limb following the naloxone still decreased resistance 47.8% ± 7.2% and 52.3% ± 3.7% below baseline levels in the innervated and denervated preparations, respectively.

Discussion

Our study demonstrates that increasing doses of the synthetic narcotics alfentanil, fentanyl, and sufentanil produce a progressive vasodilation of the peripheral vasculature in the canine hindlimb. There was no difference in effect among the drugs, and the dilation was independent of central neural input.

There has been some inconsistency in reports of the effects of these narcotics on the peripheral circulation. Previous studies have shown, for example, a decrease in systemic vascular resistance with alfentanil in animal (8–10) and human subjects (11). Yet an increase has also been reported in canine experiments (3). Similarly, fentanyl has been reported either to reduce (1,6,12,13) or have no effect (5) on peripheral vascular resistance in humans. In animal studies significant decreases in resistance have been reported in intact anesthetized dogs (14) and an initial decrease followed by an increase in resistance in a canine hindlimb preparation (15). Sufentanil has been said to

Table 1. Baseline Vascular Data Before Infusion of Opioids (mean ± SEM)

	Alfentanil		Fentanyl		Sufentanil	
	INN	DEN	INN	DEN	INN	DEN
Limb arterial pressure (mm Hg)	62.1 ±4.9	62.3 ±4.2	62.9 ±6.6	71.6 ±5.9	69.5 ±5.0	68.2 ±3.4
Limb blood flow (mL/min)	113 ±10.3	158.6[a] ±19.3	118.6 ±9.6	158.0[a] ±7.6	115.6 ±10.1	160.6[a] ±13.1
Limb vascular resistance (U)	0.51 ±0.05	0.36[a] ±0.03	0.49 ±0.06	0.42 ±0.04	0.55 ±0.06	0.39[a] ±0.03

INN, innervated limb; DEN, denervated limb.

[a] Differs significantly from innervated limb data, $P < 0.05$.

Table 2. Venous Plasma Concentrations of Narcotics in the Hindlimb at Peak Vascular Effect[a]

	Low	Medium	High	After washout[b]
Alfentanil	46 ± 12	313 ± 44	872 ± 68	5 ± 2
Fentanyl	1 ± 1	10 ± 2	28 ± 3	<1
Sufentanil	<1	4 ± 1	7 ± 1	<1

[a] Values expressed as mean ± SEM in nanograms per milliliter.

[b] Residual hindlimb venous plasma concentrations after washout of the previous narcotic at start of next narcotic study.

Table 3. Acid–Base Data Before and at Conclusion of Extracorporeal Circulation in the Isolated Hindlimb (mean ± SEM)

		Limb	
	Systemic	Innervated	Denervated
Temperature (°C)			
Baseline	38.5 ± 0.1	39.2 ± 0.1	38.6 ± 0.1
End	38.5 ± 0.1	39.2 ± 0.1	38.5 ± 0.2
Pa_{O_2} (mm Hg)			
Baseline	364 ± 6	454 ± 5	461 ± 5
End	380 ± 32	478 ± 13	484 ± 12
Pa_{CO_2} (mm Hg)			
Baseline	36.5 ± 0.3	36.7 ± 0.3	35.6 ± 0.4
End	36.5 ± 0.8	37.3 ± 0.5	35.4 ± 0.6
pH			
Baseline	7.40 ± 0.00	7.39 ± 0.00	7.40 ± 0.00
End	7.40 ± 0.02	7.38 ± 0.01	7.40 ± 0.01
Hct (%)			
Baseline	34 ± 0.3	35 ± 0.3	36 ± 0.4
End	34 ± 2.0	35 ± 0.6	34 ± 1.7

Hct, hematocrit.

be associated with sudden hypotension in patients undergoing cardiovascular surgery (16), yet also has been reported to cause little change in vascular reactivity during coronary artery surgery (4). In animal models sufentanil has either increased (17,18) or had only minimal effects (15) on systemic vascular resistance. However, the cerebral vasculature is significantly dilated by sufentanil (19).

In an elegant isolated canine muscle preparation, O'Keefe and colleagues demonstrated that any vasodilation caused by sufentanil was dependent on an intact nerve supply, particularly the α_1-adrenergic system (20). In addition, they found that central histamine receptor blockade prevented vasodilation by sufentanil beyond the level observed after denervation. Our data do not support their findings because sufentanil produced a graded vasodilation independent of neuronal integrity in our dogs.

There may be several reasons for the discrepancy. First, O'Keefe's group perfused the muscle preparation at a constant pressure, whereas our study used a constant flow. At constant pressure, myogenic forces on the vessel wall tend to maintain luminal integrity and reduce the propensity for redistribution of flow toward dilated vessels. With the constant-flow technique, as used in our study, however, any regional area of lowered resistance will tend to amplify the maldistribution of blood to the dilated area. Pressure is reduced over the entire preparation, and therefore vessels without dilation tend to collapse as critical closing pressure is approached. It may be argued that a constant-pressure model is more pharmacologically sound, but that the constant-flow technique more closely resembles the clinical situation. In our study there may have been a redistribution of flow after the infusion of the narcotics with a resultant decrease in overall vascular resistance. Second, our animals were well-anesthetized with halothane and there was no evidence of abnormal sympathetic tone. The dogs in O'Keefe's study were anesthetized with chloralose and urethane, an anesthetic technique known to increase sympathetic tone under most circumstances. Such an increase in autonomic activity in their study may have attenuated some sufentanil effects in the innervated model, but would not explain the absence of vasodilation with the opioid in their denervated experiments. Finally, their preparation was sensitive to diluent infusion in the arterial catheter so that sham injections over 3 min produced 12%–20% decreases in vascular resistance. In our model there was only a transient, insignificant dip in hindlimb arterial pressure when the diluent was infused. Possibly the sensitivity of their technique may have masked some drug-related changes in vascular resistances. Although there is no obvious explanation for the differences between our results, certainly a major portion of the difference must rest with the differences in technique.

The blood gas tensions and temperature data in our model indicate a stable preparation; hematocrits were equivalent in both limbs in the whole animal. There was no evidence of hemolysis by the roller pumps; the supernatant serum was clear when hematocrits were obtained by centrifuging. The resistance units in our study were consistent with those reported in other studies (21,22) and showed that denervation lowered calculated resistance (23). There appeared to be little drug interference from the previously administered narcotic because the blood concentrations of the other narcotics were markedly reduced by the washout (Table 2). The preparation was never used more than 1 h without a cleansing washout, which endowed the limb with long-term stability.

The use of extracorporeal circulation may alter vascular reactivity or baseline tone due to activation of complement, bradykinins, and other vasoactive humeral agents. Data from cardiopulmonary bypass show that exposure of the blood to nonendothelial tissue activates the alternative complement pathway (24). Additionally, the kallikrein cascade occurs with the production of bradykinin. The result is an increase in membrane permeability, and vasoconstriction. Because the circulation used in this model limits the extracorporeal circuit to the limb, the data obtained from cardiopulmonary bypass are not directly transferable to our study. Indeed, because the vasoactive elements activated by extracorporeal circulation are produced in the liver, lungs, and gut, it is probable that the sources for these factors are absent in our preparation and those that are indigenously present are rapidly consumed in the extracorporeal circuit due to their relatively short half-lives. Specific investigation of the potential interactions between the opioids and the physiologic changes caused by extracorporeal circulation was beyond the scope of our study.

The relationship between the effluent venous blood level and the dose of drug administered was highest for alfentanil. This variance may be explained by alfentanil's small volume of distribution and high plasma protein binding (25).

The plasma opioid concentrations measured in our animals approximate levels observed in humans during surgery. For example, the fentanyl concentrations in our dogs averaged 28 ± 3 ng/mL at peak effect after the high dose, whereas, in clinical studies, plasma concentrations of fentanyl in humans during coronary bypass surgery ranged from 11 to 29 ng/mL at skin incision (1,3). Certainly, one cannot postulate a similar vascular reactivity between the investigational dog and the arteriosclerotic human, but the progressive reduction in vascular resistance with increasing dosage of all three synthetic opioids in our animal model may help explain the sudden fall in arterial pressure and systemic vascular resistance reported in the operating room.

When naloxone was infused into the limb in the absence of an opioid, a reproducible decrease in vascular resistance was observed. The commercially available drug that we used contains methyl- and propyl-paraben; both of these preservatives will induce transient vasodilation (26). However, the antagonist did not prevent the marked decrease in resistance after high-dose fentanyl. Apparently there was little involvement by the peripheral opioid receptors with the vascular effects of the studied narcotics.

In conclusion, our study demonstrates a systemic vasodilating effect by the synthetic opioids alfentanil, fentanyl, and sufentanil in a nearly anesthetic-free isolated canine hindlimb. This effect was independent of opioid receptors and neuronal integrity. The three narcotics produced equivalent vasodilation at equivalent doses, apparently by actions directly on the smooth muscle of the peripheral arterial system.

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Vasodilator Therapy in Microembolic Porcine Pulmonary Hypertension

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McLEAN RF, PRIELIPP RC, ROSENTHAL MH, PEARL RG. Vasodilator therapy in microembolic porcine pulmonary hypertension. Anesth Analg 1990;71:35–41.

The hemodynamic effects of prostaglandin E_1, sodium nitroprusside (SNP), nitroglycerin, and hydralazine were studied in a porcine model of elevated pulmonary vascular resistance (PVR) due to glass bead microembolization (60–150-μm diameter).

Each animal received all four drugs. Each drug was titrated to produce a 30% reduction in mean systemic arterial pressure. Although all four drugs decreased PVR, distinct differences in the hemodynamic profiles of the four drugs were evident. Prostaglandin E_1 produced the largest reduction in mean pulmonary artery pressure (from 41 ± 1 to 32 ± 9 mm Hg, mean ± SEM) and PVR (25 ± 3 to 18 ± 2 mm Hg·L^{-1}·min^{-1}), and did not affect the ratio of PVR to systemic vascular resistance (PVR/SVR). Sodium nitroprusside and nitroglycerin produced moderate decreases in PVR (nitroglycerin 21 ± 2 to 18 ± 2 mm Hg·L^{-1}·min^{-1}, SNP 22 ± 2 to 19 ± 2 mm Hg·L^{-1}·min^{-1}) and in mean pulmonary artery pressure (nitroglycerin 39 ± 1 to 35 ± 1; SNP 40 ± 1 to 36 ± 2 mm Hg). Both drugs significantly increased the PVR/SVR ratio. Hydralazine was the only drug that significantly increased cardiac output (1.6 ± 0.2 to 1.9 ± 0.3 L/min). Hydralazine had no significant effect on mean pulmonary artery pressure, reduced PVR to the smallest extent (11%), and resulted in the largest increase in the PVR/SVR ratio (from 0.52 ± 0.04 to 0.80 ± 0.08).

In this model of increased pulmonary vasculature resistance prostaglandin E_1 caused an equivalent amount of pulmonary and systemic vasodilation, as expressed by the PVR/SVR ratio. Hydralazine caused the least amount of pulmonary vasodilation for a given amount of systemic vasodilation. Nitroglycerin and SNP were intermediate in their effects between prostaglandin E_1 and hydralazine.

Key Words: EMBOLISM, PULMONARY—vasodilator therapy. LUNG, EMBOLISM—vasodilator therapy.

Pulmonary hypertension may result in right ventricular dysfunction and decreased cardiac output. Vasodilators have been used in an attempt to reduce right ventricular afterload and thereby improve right ventricular function. However, beneficial hemodynamic responses to vasodilators occur in only a minority of patients, and systemic hypotension is a frequent problem (1–3). Ideally, a drug that acts preferentially on the pulmonary circulation would obviate the problem of systemic hypotension seen in these patients. Comparative evaluation of pulmonary vasodilators is difficult in the clinical setting. Recent work from this laboratory compared the effects of four vasodilators during pulmonary hypertension induced by a continuous infusion of the vasoconstrictor U46619, a thromboxane A_2 mimetic, in sheep (4).

The vasodilators we studied in the present investigation, prostaglandin E_1 (PGE_1), hydralazine, nitroglycerin, and nitroprusside (SNP), were chosen on the basis of (a) favorable reports of clinical and experimental efficacy in pulmonary hypertension (5–13); (b) drug duration of action and available formulations for intravenous administration; (c) mechanism of action via either cyclic guanosine monophosphate or cyclic adenosine monophosphate pathways; and (d) degree of specificity for systemic arterial versus systemic venous vasculature. Prostaglandin E_1 is a short-acting linoleic acid derivative that activates adenylate cyclase and increases cyclic adenosine monophosphate levels (14). Hydralazine is a long-acting smooth-muscle arterial dilator that activates guanylate cyclase (15). Nitroglycerin and SNP are short-

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acting vasodilators that activate guanylate cyclase to increase smooth-muscle guanosine 3′,5′-monophosphate (cyclic guanosine monophosphate) (15).

In our sheep study (4) PGE_1 showed the most favorable effect on the ratio of pulmonary vascular to systemic vascular resistance (PVR/SVR ratio), and hydralazine showed the least favorable effect. Sodium nitroprusside and nitroglycerin were similar to each other and were intermediate between PGE_1 and hydralazine in their effects. Because vasodilator effect may be model- and species-specific, we have studied the effect of these four vasodilators using a microemboli model of pulmonary hypertension in pigs.

Methods

Nine male pigs, weighing 15–20 kg, were anesthetized by mask inhalation of halothane in oxygen. After tracheal intubation, mechanical ventilation with halothane in oxygen with a tidal volume of 10–15 mL/kg was initiated at a rate adjusted to maintain arterial Pco_2 between 35 and 45 mm Hg. Arterial blood gas tensions were measured every 30 min, and the ventilator rate was adjusted appropriately. Sodium bicarbonate was given as required to maintain a normal base deficit (0 to −4 mEq/L). Anesthesia was maintained with halothane (1% end-tidal concentration) in oxygen. Warming blankets, radiant heaters, and a passive humidifier were used to maintain temperature at 37°–39°C. After induction of anesthesia, systemic arterial, central venous, and triple-lumen thermistor-tipped pulmonary arterial catheters were inserted through peripheral cutdowns. A 5F left atrial catheter was inserted retrogradely via the femoral artery under fluoroscopic control.

Twenty minutes after catheter placement, baseline data—including mean systemic arterial (SAP), mean pulmonary arterial (PAP), mean left atrial (LAP), and central venous (CVP) pressures, heart rate (HR), cardiac output (CO), and arterial and mixed venous blood gas tensions—were measured. Pulmonary hypertension was then induced with glass bead microemboli (60–160-μm diameter; total dose 0.5–1.0 g/kg) by administering small aliquots (1–1.5 g) every 5–10 min through the central venous catheter until cardiac output decreased to 70% of baseline and remained at that level for 10 min. Measurements were made immediately after completion of embolization and 30 and 60 min later. Infusions of PGE_1, SNP, and nitroglycerin were then administered in random order. Each infusion was titrated to reduce SAP to 70% of the predrug value. Measurements were made immediately before drug administration and after 15 min at a stable drug-infusion rate. Forty-five minutes were allowed between drug infusions for hemodynamic stabilization and clearance of drug effect. Forty-five minutes after the last drug infusion, hydralazine was given over a 10–15-min period in 3-5-mg boluses to reduce SAP to 70% of the predrug level; a final set of measurements was then made.

Intravascular pressures were measured with Hewlett-Packard quartz transducers (model 1290A) and recorded on a Hewlett-Packard eight-channel recorder. Arterial and venous blood gas tensions were measured using a Corning 168 pH/blood gas analyzer. Venous and arterial oxygen saturations were calculated using a Severinghaus slide rule (16), assuming a P_{50} value of 30.6 mm Hg for porcine hemoglobin (17). Hemoglobin was measured using an IL 282 cooximeter. Shunt fraction was calculated as (capillary oxygen content − arterial oxygen content)/(capillary oxygen content − mixed venous oxygen content). Oxygen content (in milliliters per 100 mL of blood) was calculated as ([Hb] × 1.34 × saturation + 0.003 × Po_2), where [Hb] is the concentration of hemoglobin. Cardiac output was determined in triplicate by thermodilution using 10 mL of iced saline injectate; the Edwards 9520A CO computer was used. Pulmonary vascular resistance (PVR) was calculated as (PAP − LAP)/CO, SVR as (SAP − CVP)/CO, stroke volume (SV) as CO/HR, right ventricular (RV) stroke work as SV × (PAP − CVP) × 0.0136 g-m. The ratio of PVR to SVR was calculated to quantify the degree of pulmonary vasodilation occurring for a given amount of systemic vasodilation.

Statistical analysis. Effects of embolization were assessed using a one-way repeated measures analysis of variance of four time points (baseline, immediately postemboli, 30 min postemboli, 60 min postemboli). The Newman-Keuls' multiple comparison test was used to identify differences between time points. The stability of the model over the 3–4-h period of the drug studies was similarly assessed by a one-way repeated measures analysis of variance of the four predrug values (first drug, second drug, third drug, and fourth drug in order). Differences among drug effects were analyzed by a one-way repeated measures analysis of variance using the four drug values. To assess the effect of order of administration, the three drugs that were given in random order (SNP, nitroglycerin, PGE_1) were blocked according to order of administration and subjected to repeated measures analysis of variance.

Table 1. Hemodynamic Variables at Selected Time Points Throughout the Study

	PAP	SAP	CO	HR	SV	PVR	SVR	PVR/SVR
Baseline	19 ± 1	81 ± 3	2.21 ± 0.16	123 ± 7	18.1 ± 1.0	4.9 ± 6	34.4 ± 2.9	0.14 ± 0.015
Postemboli	43 ± 1^a	73 ± 3^a	1.53 ± 0.19^a	160 ± 9^a	9.5 ± 0.9^a	25.4 ± 2.9^a	43.4 ± 3.9^a	0.58 ± 0.035^a
30 min postemboli	42 ± 1^a	73 ± 4^a	1.53 ± 0.22^a	159 ± 8^a	9.7 ± 1.3^a	24.9 ± 2.8^a	45.1 ± 4.5^a	0.53 ± 0.028^a
Predrug 1	41 ± 1^a	75 ± 3^a	1.48 ± 0.47^a	162 ± 9^a	9.7 ± 1.0^a	24.2 ± 2.5^a	46.2 ± 5.2^a	0.50 ± 0.012^a
Predrug 2	40 ± 1^a	75 ± 4^a	1.60 ± 0.17^a	166 ± 14^a	9.9 ± 1.0^a	22.5 ± 2.7^a	46.6 ± 4.9^a	0.50 ± 0.035^a
Predrug 3	40 ± 1^a	74 ± 4^a	1.60 ± 0.17^a	168 ± 9^a	10.5 ± 1.1^a	21.9 ± 2.3^a	42.7 ± 4.5^a	0.52 ± 0.041^a
Predrug 4	38 ± 2^a	69 ± 3^a	1.70 ± 0.18^a	167 ± 10^a	10.5 ± 1.2^a	20.4 ± 2.0^a	39.7 ± 3.5^a	0.52 ± 0.036^a

SAP, mean systemic arterial pressure (mm Hg); PAP, mean pulmonary artery pressure (mm Hg); CO, cardiac output (L/min); HR, heart rate (beats/min); SV, stroke volume (mL/beat); PVR, pulmonary vascular resistance (mm Hg·min·L^{-1}); SVR, systemic vascular resistance (mm Hg·min/L^{-1}); PVR/SVR, pulmonary vascular resistance to systemic vascular resistance ratio.

Values are mean ± SEM of nine pigs.

$^aP < 0.01$ vs baseline.

Table 2. Pulmonary Hemodynamic Variables With Drug Therapy

	PAP	LAP	CO	PVR	PVR/SVR	RVSW	RV work
Pre-PGE$_1$	41 ± 1	7.4 ± 7	1.5 ± 0.2	24.7 ± 3.0	0.54 ± 0.032	4.1 ± 0.6	539 ± 88
Post-PGE$_1$	32 ± 1.4^a	7.5 ± 1	1.5 ± 0.19	17.8 ± 2.0^a	0.58 ± 0.041	3.8 ± 0.6	508 ± 73
Pre-NTG	39 ± 1.1	7 ± 1	1.6 ± 0.15	21.4 ± 1.8	0.49 ± 0.026	4.2 ± 0.5	675 ± 82
Post-NTG	35 ± 1.3^a	7 ± 1	1.6 ± 0.2	18.5 ± 1.6^a	0.64 ± 0.048^a	3.9 ± 0.6	620 ± 97
Pre-SNP	40 ± 1.4	8 ± 1	1.6 ± 0.19	22.2 ± 2.5	0.49 ± 0.035	4.0 ± 0.5	664 ± 99
Post-SNP	36 ± 1.6^a	7 ± 1	1.7 ± 0.21	19.1 ± 2.1^a	0.62 ± 0.061^a	3.9 ± 0.6	656 ± 105
Pre-HYD	38 ± 1.6	8 ± 1	1.6 ± 0.2	20.4 ± 2.0	0.52 ± 0.036	3.9 ± 0.7	633 ± 93
Post-HYD	38 ± 1.7	7 ± 1	1.9 ± 0.26^b	18.2 ± 2.3^a	0.85 ± 0.083^a	4.4 ± 0.7	758 ± 125

PAP, mean pulmonary artery pressure (mm Hg); LAP, mean left atrial pressure (mm Hg); CO, cardiac output (L/min); PVR, pulmonary vascular resistance (mm Hg·min·L^{-1}); PVR/SVR, pulmonary vascular resistance to systemic vascular resistance ratio; RVSR, right ventricular stroke work (g·m·beat^{-1}); RV work, right ventricular work in g-m; PGE$_1$, prostaglandin E$_1$; NTG, nitroglycerin; SNP, sodium nitroprusside; and HYD, hydralazine.

Values are mean ±SEM for nine pigs.

$^aP < 0.01$ vs predrug value.

$^bP < 0.5$ vs predrug value.

Results

Embolization increased PAP 225%, increased PVR 500%, decreased CO 27%, increased HR 30%, decreased SV 48%, and decreased SAP 10% (Table 1). The hemodynamic changes seen with embolization persisted and remained stable throughout the time-course of the study. Arterial P_{O_2} decreased 48% and shunt fraction increased 37% with embolization.

Drug dosages were 23 ± 7 ng·kg^{-1}·min^{-1} for PGE$_1$, 38 ± 7 μg·kg^{-1}·min^{-1} for nitroglycerin, 10 ± 3 μg·kg^{-1}·min^{-1} for SNP, and 0.37 ± 0.15 mg/kg for hydralazine. Tables 2–4 present the drug effects on hemodynamic and gas exchange variables. All four drugs produced equivalent reductions in SAP (25%–30%). Prostaglandin E$_1$ significantly decreased PAP, PVR, SVR, and HR, and significantly increased SV. Prostaglandin E$_1$ did not affect CO, the PVR/SVR ratio, RV work, or RV stroke work. It increased shunt fraction, but mixed venous P_{O_2} and arterial P_{O_2} were not significantly affected. Nitroglycerin and SNP were similar to each other in their effects. Both significantly decreased SAP, PAP, PVR, and SVR, and increased the PVR/SVR ratio. Neither drug significantly affected CO, SV, RV work, or RV stroke work. Neither drug significantly affected shunt fraction, arterial P_{O_2}, or mixed venous P_{O_2}. Hydralazine decreased SAP, PVR, and SVR, and increased CO, SV, and the PVR/SVR ratio. Hydralazine did not significantly affect HR. It increased shunt fraction and mixed venous P_{O_2} without affecting the arterial P_{O_2}.

Although the pulmonary hemodynamic effects of PGE$_1$, SNP, and nitroglycerin were similar (decreased PAP, decreased PVR, and unchanged CO), the decreases in PAP and PVR with PGE$_1$ were significantly greater than those with the other drugs. Prostaglandin E$_1$ was the only drug that decreased HR; this effect was significantly different from the other drugs ($P < 0.01$ for hydralazine; $P < 0.05$ for nitroglycerin and SNP). Figure 1 illustrates the effect on PAP of the four drugs. Figure 2 illustrates the change in the PVR/SVR ratio with drug administration. Hydralazine was the only drug to increase CO and mixed venous P_{O_2}; these effects were significantly different from the other three drugs ($P < 0.01$).

Table 3. Systemic Hemodynamic Variables With Drug Therapy

	SAP	CVP	CO	HR	SV	SVR
Pre-PGE_1	73 ± 3.9	10 ± 1	1.5 ± 0.2	161 ± 9	9.7 ± 1.2	45.8 ± 5.7
Post-PGE_1	53 ± 2.5^a	9 ± 1^b	1.5 ± 0.19	137 ± 8^a	11.6 ± 1.5^a	31.3 ± 3.5^a
Pre-NTG	75 ± 4	9 ± 1	1.6 ± 0.15	167 ± 12	9.8 ± 1	44.2 ± 4.3
Post-NTG	53 ± 2.9^a	8 ± 1	1.6 ± 0.2	161 ± 11	10.4 ± 1.1	29.4 ± 2.5^a
Pre-SNP	76 ± 3	9 ± 1	1.6 ± 0.19	168 ± 10	9.5 ± 1	45.5 ± 4.5
Post-SNP	56 ± 2.2^a	7 ± 1^a	1.7 ± 0.21	173 ± 11	9.7 ± 1	31.6 ± 3.0^a
Pre-HYD	69 ± 3	10 ± 1	1.6 ± 0.2	167 ± 10	9.9 ± 1.4	39.8 ± 3.6
Post-HYD	49 ± 3.3^a	10 ± 1	1.9 ± 0.26^b	173 ± 10	11.3 ± 1.4^b	21.5 ± 1.8^a

SAP, mean systemic arterial pressure (mm Hg); CVP, central venous pressure (mm Hg); CO, cardiac output (L/min); HR, heart rate (beats/min); SV, stroke volume (mL/beat); SVR, systemic vascular resistance (mm Hg·min·L^{-1}); PGE_1, prostaglandin E_1; NTG, nitroglycerin; SNP, sodium nitroprusside; and HYD, hydralazine.

Values are mean ± SEM for nine pigs.

$^a P < 0.01$ vs predrug value.

$^b P < 0.05$ vs predrug value.

Table 4. Arterial, Mixed Venous Po_2, and Shunt Fraction at Various Points Throughout the Study

	Arterial Po_2 (torr)	Venous Po_2 (torr)	Shunt (%)
Baseline	423 ± 20	47 ± 2	13.5 ± 1.2
60 min postemboli	218 ± 42^a	34 ± 2^a	18.5 ± 2.4
Pre-PGE_1	180 ± 43	33 ± 2	19.46 ± 2.6
Post-PGE_1	163 ± 49	32 ± 2	24.81 ± 4.1^a
Pre-NTG	209 ± 42	35 ± 2	19.53 ± 3.3
Post-NTG	212 ± 41	33 ± 2	18.74 ± 3.1
Pre-SNP	171 ± 40	33 ± 2	20.66 ± 2.8
Post-SNP	152 ± 31	32 ± 2	22.8 ± 2.8
Pre-HYD	160 ± 37	31 ± 1	21.39 ± 3.2
Post-HYD	140 ± 37	36 ± 3^a	26.39 ± 3.5^a

PGE_1, prostaglandin E_1; NTG, nitroglycerin; SNP, sodium nitroprusside; and HYD, hydralazine.

Values are mean ± SEM for eight pigs.

$^a P < 0.01$ compared with corresponding value (baseline or predrug).

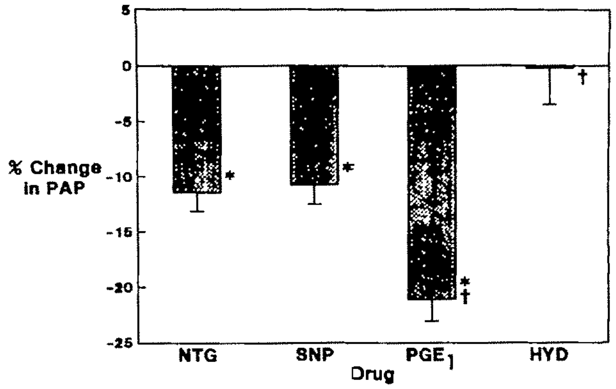

Figure 1. Effects of each of the four drugs on PAP when given in amounts adequate to reduce SAP to 70% of the predrug value. Values are expressed as the mean percent change in PAP ± SEM in nine animals. $*P < 0.01$ vs predrug value. $†P < 0.05$ vs each of the other three drugs. NTG, nitroglycerin; HYD, hydralazine.

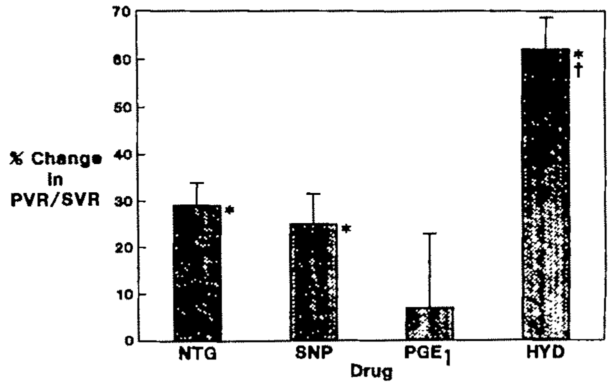

Figure 2. Effect of drug administration on the PVR/SVR ratio. All values are expressed as mean percent change ± SEM in nine animals. $*P < 0.01$ vs predrug value. $†P < 0.05$ vs each of the other three drugs. NTG, nitroglycerin; HYD, hydralazine.

Discussion

The increase in PVR that occurs with microembolization is due to a combination of mechanical obstruction of the pulmonary vascular bed and active pulmonary vasoconstriction from humoral or neural factors (18,19). Embolization with glass beads less than 180 μm in diameter results in arterial vasoconstriction and, to a lesser extent, in venoconstriction. The maximal response is seen in the 100–200-μm diameter arterioles upstream from the site of embolization (20). Shunt fraction and total lung water increase with pulmonary microembolization (18,21), and the resultant hypoxia may further increase PVR through hypoxic pulmonary vasoconstriction. In dogs, the elevation in PVR seen with microembolization has been found to be stable for at least 60 min (18). In the current study, elevations in PVR and PAP remained stable throughout the duration of the study (3–4 h). Because drug therapy resulted in decreases in both PAP and PVR, some degree of reversible pulmonary vasoconstriction was present. Although glass bead microembolization is *not* a clinical phenomenon, the mechanisms of pulmonary hypertension involved *are* (obliteration of pulmonary bed, hypoxia, thrombosis with release of humoral factors). The stability of the model and the presence of reversible pulmonary vasoconstriction lead us to believe that it is a valid model for comparing pulmonary vasodilator effects. The close relationship between this model and the sheep model with respect to the pulmonary specificity of the individual drugs supports this concept. Halothane was chosen as anesthetic because of its ease of administration and titration. Although there is evidence that halothane may affect hypoxic pulmonary vasocontriction, there is considerable controversy about this (22). We know of no evidence that halothane alters the pharmacologic action of any of the four drugs studied. It was present in equal concentration throughout the experiment.

Selective reduction of PVR is one goal of pulmonary vasodilator therapy. Rich et al. (23) considered the ideal pulmonary vasodilator response to include a decrease in PVR that exceeds the decrease in SVR. In the current study, we used the PVR/SVR ratio to assess the relationship between changes in PVR and SVR. A decrease in the ratio implies that pulmonary vasodilation has exceeded systemic vasodilation.

In this study, the four drugs demonstrated distinct differences in their hemodynamic profiles. Hydralazine was the only agent to significantly increase CO in this model. However, hydralazine also produced the largest increase in the PVR/SVR ratio and did not affect PAP. Hydralazine causes reflex sympathetic activation (24) and may also act as a direct inotropic agent (25). The increase in CO with hydralazine may have been due to (a) decreased RV afterload from pulmonary vasodilation; (b) indirect or direct inotropic/chronotropic effects on the heart; (c) reduction in SVR; or (d) selective systemic arterial (versus venous) vasodilation. It seems unlikely that the increase in CO seen with hydralazine is due to superior pulmonary vasodilating effects. In this model, hydralazine resulted in the least degree of pulmonary vasodilation, both as indicated by the lack of change in PAP and the increase in the PVR/SVR ratio. Hydralazine is a selective systemic arterial vasodilator, whereas the other three drugs are balanced systemic vasodilators (26). The reduction in CVP seen with PGE_1 and SNP was significantly different from the effect seen with hydralazine ($P < 0.05$). The systemic venodilator effects of PGE_1 and SNP may have reduced venous return and prevented the increase in CO that should have occurred from reduced left and right ventricular afterload. The concomitant administration of intravenous fluids with these drugs might have increased CO to the levels seen with hydralazine. In a similar pulmonary embolization model in dogs, hydralazine increased CO but did not change PAP (5). Despite initial favorable reports (8,27) of improvement with oral hydralazine, severe hypotension, exacerbation of pulmonary hypertension, and even death have occurred with its use in patients (10,28–30).

Nitroglycerin has been used clinically in the treatment of pulmonary hypertension (9,11). Earlier work in an oleic acid model suggested that nitroglycerin was a more specific and effective pulmonary vasodilator than SNP (6); however, there were no significant differences between the two drugs in this study. Both drugs reduced PVR and PAP, but they also increased the PVR/SVR ratio. However, the increase in PVR/SVR ratio with these drugs was significantly less than that seen with hydralazine, suggesting that these drugs are more useful pulmonary vasodilators than hydralazine.

Prostaglandin E_1 differs from the other drugs used in this study because of its rapid pulmonary clearance. There is a 92% first-pass elimination of PGE_1 in guinea pig lung (31). Similar rates of clearance have been noted in dogs, cats, and rabbits (31). The rapid clearance is presumably effected by pulmonary parenchymal 15-hydroxyprostaglandin dehydrogenase. The liver also metabolizes PGE_1 to a considerable extent (32). However, PGE_1 metabolism may not be normal in diseased lungs (33), although it is a potent and effective pulmonary vasodilator in patients with pulmonary hypertension secondary to mitral valve disease (12). Prostaglandin E_1 has been studied in patients who were undergoing mitral valve replacement in whom weaning from cardiopulmonary bypass was complicated by pulmonary hypertension. Prostaglandin E_1 was found to significantly decrease PAP and PVR and increase CO, thereby allowing patients to be weaned from cardiopulmonary bypass (34). Prostaglandin E_1 has been found to be effective in lowering PAP after repair of congenital heart lesions in children (35). In the current study, PGE_1 resulted in the largest decreases in PVR and PAP and was the only drug that did not increase the PVR/SVR ratio. Pulmonary metabolism of PGE_1 may be the reason for the beneficial effect on the PVR/SVR ratio. Significant reductions in SVR and SAP occurred, suggesting that significant amounts of PGE_1 survived passage through the pulmonary circulation.

A comparison of the changes in the PVR/SVR ratio in this model and in the sheep model with administration of these drugs to the same reduction to SAP is shown in Figure 3. It can be seen that there is a close correlation between the two models with respect to the effect of each of the four drugs on the PVR/SVR ratio. This suggests that the relative pulmonary vasodilator effect of these drugs is not solely model- or species-dependent. In addition, these animal results are in general consistent with clinical impressions (2).

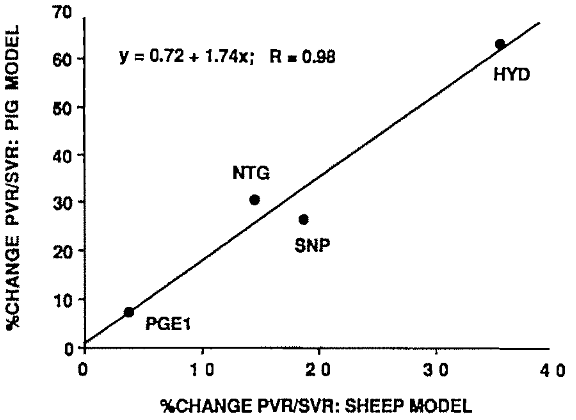

Figure 3. Plot of percent change in PVR/SVR ratio with drug administration in the pig model vs the percent change in PVR/SVR seen in the sheep model. NTG, nitroglycerin; HYD, hydralazine.

However, care must be taken in extrapolating the findings of this study to the clinical situation. Both this model and the sheep model of pulmonary hypertension have limitations. Human pulmonary hypertension can result from a wide variety of causes and can be associated with a wide range of pathologic abnormalities. Drugs in this experiment were given in amounts adequate to produce a given reduction in SAP. We are thus unable to comment on the dose-response curves of each of these drugs. It is possible that effects may be different if the drugs are administered over a broader range. The response of any given patient with pulmonary hypertension to a systemic vasodilator is often unpredictable. Pulmonary vasodilator therapy should be based on baseline hemodynamic variables, and administration should be titrated to achieve closely monitored desired effects on HR, blood pressure, PAP, and arterial oxygen content.

In conclusion, in this porcine model, as in the sheep model, PGE_1 caused the greatest amount of pulmonary vasodilation for a given degree of systemic vasodilation. Sodium nitroprusside and nitroglycerin both decreased PVR and PAP, but they also increased the PVR/SVR ratio, suggesting less pulmonary vasodilation for a given degree of systemic vasodilation than was seen with PGE_1. Hydralazine was the only drug to increase CO in this model, but was associated with the least favorable balance between pulmonary and systemic vasodilation of the four drugs. Hydralazine resulted in the largest increase in the PVR/SVR ratio and did not decrease PAP.

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Effect of Umbilical Perfusate pH and Controlled Maternal Hypotension on Placental Drug Transfer in the Rabbit

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GAYLARD DG, CARSON RJ, REYNOLDS F. Effect of umbilical perfusate pH and controlled maternal hypotension on placental drug transfer in the rabbit. Anesth Analg 1990;71:42–8.

The purpose of this study was to explore the effect that fetal acidosis and poor maternal placental blood flow may have on the rate of passage across the placenta of drugs commonly used in labor: bupivacaine and meperidine. The rabbit placenta perfused in situ on the fetal side was used, and antipyrine (phenazone) was included as an index of placental exchange and of maternal placental flow. Bupivacaine and meperidine (both 1.25 mg/mL) and antipyrine (4 mg/mL) were infused into a maternal external jugular vein, at 3 mL/h, after loading, in seven anesthetized does. A single placenta in each doe was perfused via the umbilical arteries with Krebs' bicarbonate buffer at pH 7.5 (phase 1), 7.0 (phase 2), and 7.5 (phases 3–5). During phase 4 maternal blood was withdrawn so as to reduce maternal arterial pressure by 35%, and in phase 5 it was reinfused. Concentrations of drugs were measured during each of the five phases in maternal arterial plasma (C_{ma}) and in the effluent perfusate collected from the umbilical vein (C_{uv}). From these data, placental clearance rates ($C_{uv} \times$ umbilical flow/C_{ma}) were calculated for each drug at each phase. Clearance of bupivacaine and meperidine increased ($P < 0.03$) during phase 2, whereas that of antipyrine did not. Clearance of meperidine and antipyrine, but not of bupivacaine, decreased during phase 4. If these results can be extrapolated to the clinical situation, they suggest that the adverse effects of drugs may well be exacerbated in the presence of fetal compromise.

Key Words: PLACENTA, DRUG TRANSFER—meperidine, bupivacaine. ANESTHESIA, OBSTETRICAL—placental transfer.

If a drug is given acutely to a parturient, its transfer rate determines the dose received by the fetus, and the equilibrium fetal/maternal plasma concentration (F/M) ratio reflects both transfer rate and the ultimate amount of drug in the fetal compartment. Thus both transfer rates and equilibrium F/M ratios of drugs used in labor are important determinants of the magnitude of the potential neonatal effects.

Human studies of placental drug transfer have usually been limited to measurement of drug concentrations in umbilical cord, commonly umbilical vein, and maternal plasma at delivery. From these measurements one derives the umbilical venous (UV) to maternal plasma concentration ratio, but little information can be gained about the rate of drug transfer, nor can one be certain that equilibrium has been attained. Moreover, in the clinical setting it is not possible to study the various factors that may affect transplacental drug distribution, and animal models in which conditions can be carefully controlled and varied must be employed.

Particles cross the placenta in a number of ways: for example, amino acids and iodine cross by active transport (1,2), a process requiring metabolic energy that can take place against a concentration gradient, whereas dextrose crosses by facilitated diffusion, which, although selective, is not energy-consuming and occurs only down a concentration gradient, but at a faster rate than physical laws alone would permit (3). It has long been acknowledged that foreign substances, such as drugs used for anesthesia and analgesia, cross the placenta by passive diffusion (4), a simple process dependent on concentration gradient. Placental transfer has traditionally been used as a generic term (5–7) to cover all these processes of maternal-fetal exchange.

The transfer of polar drugs, which penetrate lipid

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membranes slowly, is said to be permeability-dependent and is inversely related to molecular size (8), whereas diffusion of lipid-soluble drugs, which freely penetrate lipid membranes, is termed flow-dependent transfer. In other words, the rate of diffusion of lipophylic drugs is not affected by their molecular weight, but is strongly influenced by placental blood flow because the latter helps to maintain the concentration gradient. Such has been demonstrated for lidocaine, bupivacaine, meperidine, fentanyl, and anticonvulsant drugs whose transfer rates all rise with umbilical blood flow (9–12). Such drugs, however, are partially bound to plasma proteins, and their transfer rates depend also on their binding on either side of the placenta (10) because this determines the gradient for the freely diffusible unbound moiety of the drug. All this evidence attests to a passive process, one not influenced by competition or saturation as active transport would be.

The process of passive diffusion dictates that drugs cross lipid membranes principally in the unbound nonionized state. Thus at equilibrium it is the gradient of the free nonionized fraction that is minimized, and different concentrations of binding protein in fetal and maternal plasma affect not only transfer rate but also equilibrium ratio (13,14). There is also a pH gradient across the placenta and a basic drug will ionize more in the more acidic fetal compartment, thus promoting transfer of the free base to the fetus and increasing the equilibrium F/M ratio. It can be predicted from the Henderson–Hasselbalch equation that the more severe the fetal acidosis the more a basic drug will become concentrated in the fetal compartment (3). This phenomenon is known as ion-trapping. Fetal acidosis has indeed been associated with an increase in F/M ratio of bupivacaine in sheep (15,16) and humans (17), but it is not known whether ion-trapping affects the rate of drug transfer or only the final equilibrium distribution.

It might be assumed that maternal placental blood supply would also affect the speed with which the fetus acquires drugs given acutely to the mother, but this effect has not hitherto been evaluated. Maternal placental flow is essentially passive and therefore dependent on maternal cardiac output and arterial pressure (18). Consequently, it is liable to fall as a result of blood loss.

The small animal placenta, perfused in situ on the fetal side via the umbilical vessels, is a preparation that was first described in 1960 by Money and Dancis (19) for physiologic studies, but was more recently adapted by this laboratory for the study of drug transfer (9) because it allows the actual transfer rate to be measured, under conditions that can be varied. We have used the rabbit placenta, perfused in situ, to study the effect of artificial fetal acidosis and of maternal hypotension on the transfer of bupivacaine and meperidine. Antipyrine was included as an index of placental exchange (20).

Method

The experiments were performed under Home Office Project Licence No. 90/00057. Seven pregnant New Zealand white rabbits (4.67 ± 0.4 kg, mean ± SD) were studied within 4 days of term (gestation = 30 days).

Preparation of the Doe

Anesthesia was induced via a Butterfly needle in a marginal ear vein, using alphaxalone/alphadalone, and maintained with 25% ethyl carbamate (urethane) given intravenously as required. The doe lay on a warming blanket and breathed oxygen-enriched air spontaneously via a tracheostomy. A carotid artery was cannulated for continuous blood pressure monitoring and for maternal blood sampling for drug and blood gas analysis. Bupivacaine (1.25 mg/mL), meperidine (1.25 mg/mL), and antipyrine (4 mg/mL) were infused into a maternal external jugular vein at a rate of 12 mL/h for 20 min, 6 mL/h for 1 h, and 3 mL/h thereafter, a regimen previously shown to produce a relatively constant maternal plasma drug concentration (21).

Preparation of a Placenta

Once the maternal intravenous infusion of drugs was in progress, the doe's abdomen was incised in the midline and a single fetal sac opened. The two umbilical arteries and the single umbilical vein were cannulated toward the placenta and the fetus was removed. The fetal side of the placenta was perfused artificially at 1 mL/min via the two arteries with Krebs' bicarbonate buffer containing 1.5% dextran (molecular weight, 40,000) to maintain the oncotic pressure, and the effluent perfusate was collected from the umbilical vein. The exposed section of uterus was kept warm and moist by shining a lamp on it after covering it with a clear plastic sheet that acted like a greenhouse.

Table 1. Maternal Physiologic Data

	n	Initial	Final
MAP (mm Hg)	7	84 ± 12	90 ± 16
Maternal pH	7	7.47 ± 0.04	7.43 ± 0.04
Pao_2 (mm Hg)	7	112 ± 40	141 ± 20
$Paco_2$ (mm Hg)	7	26.6 ± 2.5	17.8 ± 2.7

MAP, mean arterial pressure.
All data are mean ± SD.

Table 2. Weights of Does, Fetuses, and Placentas

	n	Weight (g)
Does	7	4670 ± 410
Fetuses	7	33.2 ± 7.8
Placentas	7	5.44 ± 1.53

All data are mean ± SD.

Experimental Procedure

Maternal blood gases were measured at the beginning and end of the placental perfusion.

During phase 1, the composition of the Krebs' buffer, which was designed to be physiologic, was (in mmol/L) NaCl, 118.4; KCl, 4.75; $NaHCO_3$, 25.0; $MgSO_4$, 1.23; KH_2PO_4, 1.2; $MgCl_2$, 1.28; and $CaCl_2$, 2.55, in distilled water and gassed continuously with 5% carbon dioxide in oxygen at 37°C.

During phase 2, acidic Krebs' buffer (made by reducing the content of $NaHCO_3$ to 6.25 mmol/L) was perfused.

During phases 3–5, the "physiologic" Krebs' buffer was again perfused.

During phase 4, maternal hypotension was induced by withdrawing blood from the arterial cannula into a heparinized syringe until the maternal mean arterial pressure was 65% of the baseline level.

In phase 5, maternal blood volume was restored by reinfusion of the withdrawn blood.

During each phase, after discarding the first 5 mL of effluent placental perfusate, two collections of at least 5 mL were made from the umbilical vein, and maternal arterial blood was sampled during each collection.

A further 20 mL of maternal blood was taken at the end of the experiment for estimation of protein binding by ultrafiltration (22). The removed fetus and perfused placenta were weighed after the experiment.

Drug Analysis

Concentrations of bupivacaine, meperidine, and antipyrine were measured in effluent umbilical perfusate (sample volume, 1 mL), maternal arterial plasma (0.25 mL), and plasma ultrafiltrate (0.5 mL, to measure the concentration of *free* drug) by gas chromatography as described elsewhere (9,23).

Calculation of Transfer Rate

One important determinant of placental diffusion, the maternal concentration of diffusible drug, is itself determined by the experimenter and is not a function of drug or placenta. It is therefore appropriate to use an expression such as placental clearance, which takes account of this. Placental clearance (Cl) is the volume of maternal blood cleared of drug by the umbilical circulation in unit time, and may be calculated as the rate of drug transfer divided by the maternal concentration:

$$\mathrm{Cl} = Q_u (C_{uv} - C_{ua})/C_{ma} \text{ (mL/min)},$$

where Q_u = umbilical flow (mL/min), C_{uv} = umbilical vein concentration (μg/mL), C_{ua} = umbilical artery concentration, and C_{ma} = maternal arterial concentration. As in the present experiment, the Krebs' buffer perfused into the umbilical artery contained no drug, $C_{ua} = 0$, and $Q_u = 1$ mL/min:

$$\mathrm{Cl} = C_{uv}/C_{ma} \text{ (mL/min)}.$$

Placental uptake of drug decreases the apparent clearance only in the first collection (which was discarded) of any phase of the experiment (9) and was therefore neglected.

Results are expressed where appropriate as mean ± SD. The differences between the clearance values at each phase of the experiment were compared using Student's paired *t*-test.

Results

Maternal physiologic data recorded at the beginning and the end of the experiments are given in Table 1. The final value of mean arterial pressure did not differ significantly from the baseline value. In phase 4, in order to reduce mean arterial pressure by 35%, between 30 and 70 mL (mean, 48 ± 12 mL) of arterial blood was withdrawn. Maternal Pao_2 increased significantly ($P < 0.05$) and $Paco_2$ decreased significantly ($P < 0.05$) between the beginning and the end of the experiment. The weights of the does, fetuses, and placentas are given in Table 2. These were appropriate for gestation. The mean pH of the "physiologic" Krebs' buffer was 7.52 ± 0.067 and of the acidic buffer, 7.02 ± 0.081.

Table 3. Physicochemical Data

	pK_a	Partition coefficient[a]	Protein binding (%)	Molecular weight
Antipyrine	1.4	1.7	0	188
Meperidine	8.7	18	22.0 ± 10.2[b] (n = 5)	247
Bupivacaine	8.1	257	77.1 ± 11.9[b] (n = 6)	288

[a] Oleyl alcohol/buffer pH 7.4 (9).
[b] Data are mean ± SD.

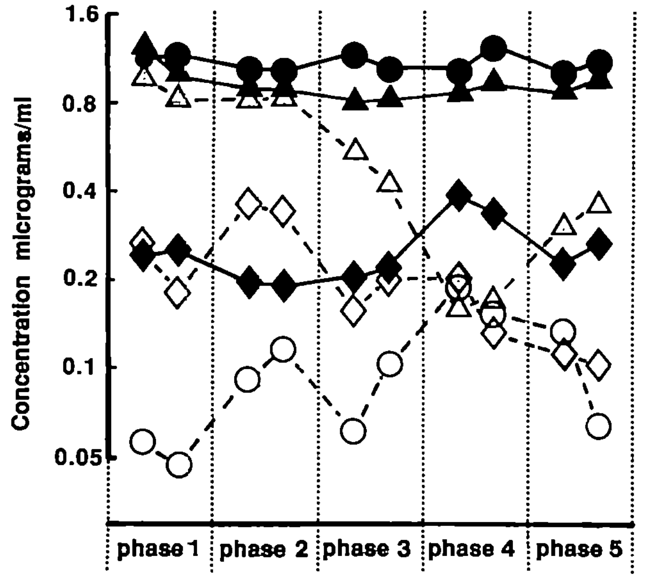

Figure 1. Concentrations (log scale) of antipyrine (*triangles*), bupivacaine (*circles*), and meperidine (*diamonds*) in maternal arterial plasma (*filled symbols*) and effluent perfusate (*open symbols*) in a single experiment. For description of phases see text.

Table 3 gives physicochemical characteristics of the three drugs (all bases) and their protein binding in these does. The pK_a values dictate that meperidine is 96% ionized at pH 7.4, whereas bupivacaine is 83% ionized and antipyrine is virtually nonionized. Protein binding increased with partition coefficient and is consistently lower in the rabbit than in humans (10), although showing the same rank order.

Figure 1 shows the drug concentrations in maternal arterial plasma and umbilical venous effluent perfusate in a typical experiment. As total maternal plasma clearance of these drugs varies widely in rabbits (9), mean concentrations are not presented. A mean clearance value was calculated from the paired data for each phase of each experiment.

Table 4 shows the mean placental clearance, derived from all seven experiments, of each drug during each phase. From the protein binding data for each doe, the maternal free drug concentrations and the placental clearance values of free drug were calculated (Table 5). Numbers are incomplete, as protein binding could not be measured in every doe. During the baseline period (phase 1) and during phases 3 and 4 there was no significant difference in clearances between meperidine and antipyrine, whereas bupivacaine clearance was markedly lower during all phases. These are consistent findings at a perfusate flow rate of 1 mL/min (9–11). During perfusion with acidic buffer (phase 2), clearance of both bupivacaine and meperidine rose significantly ($P < 0.03$), whereas that of antipyrine did not (Figure 2). During phase 3, clearances of bupivacaine and meperidine returned to levels that did not differ significantly from the baseline (phase 1).

Clearance values after removal of maternal blood (phase 4) and its reinfusion (phase 5) are also shown in Table 4; the percentage changes from phase 3 are shown in Figure 3. During maternal hypotension, the mean clearance of antipyrine decreased significantly ($P < 0.01$), and after reinfusion of maternal blood it increased significantly ($P < 0.03$) but did not return to baseline level. The mean clearance of meperidine was reduced to a lesser extent during hypotension, but the change was still significant ($P < 0.03$). There was no significant recovery after restoration of maternal circulating blood volume. The mean clearance of bupivacaine increased, although not significantly, during hypotension, and there was minimal change after restoration of maternal blood.

Discussion

The relevance of this model to the human has been discussed elsewhere (9). The small animal placenta perfused in situ is a useful tool for measuring placental transfer rate and the factors affecting it. The rabbit placental membrane is a thin hemochorial type (24) and therefore, for the purposes of lipid diffusion, comparable to the human. The flow pattern in the rabbit, however, is countercurrent, whereas that in the human behaves more like a concurrent system (3). The more efficient countercurrent system permits a greater degree of equilibration across the placental membrane in a single circuit of the placental bed.

Whether or not drugs approach equilibrium across the placenta in a single circuit, this equilibration should not be confused with that throughout the fetal compartment, which takes many minutes or even hours (23,25). Eliminating the fetal compartment, as in the present model, simplifies the study of transfer rate.

Equilibrium F/M plasma ratios of basic drugs such as local anesthetics are quite predictably affected by

Table 4. Placental Clearance of Total Drug (mL/min)

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Antipyrine (n = 7)	0.795 ± 0.145	0.520 ± 0.262	0.561 ± 0.257	0.127 ± 0.065	0.270 ± 0.102
Meperidine (n = 7)	0.726 ± 0.247	1.31 ± 0.421	0.501 ± 0.232	0.260 ± 0.125	0.324 ± 0.068
Bupivacaine (n = 7)	0.054 ± 0.013	0.133 ± 0.032	0.060 ± 0.015	0.096 ± 0.053	0.085 ± 0.044

All data are mean ± SD.

Table 5. Placental Clearance of Unbound Drug (mL/min)

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Antipyrine (n = 7)	0.795 ± 0.145	0.520 ± 0.262	0.561 ± 0.257	0.127 ± 0.065	0.270 ± 0.102
Meperidine (n = 6)	0.991 ± 0.291	1.69 ± 0.536	0.666 ± 0.254	0.295 ± 0.163	0.406 ± 0.082
Bupivacaine (n = 5)	0.302 ± 0.213	0.722 ± 0.448	0.384 ± 0.328	0.537 ± 0.644	0.431 ± 0.378

All data are mean ± SD.

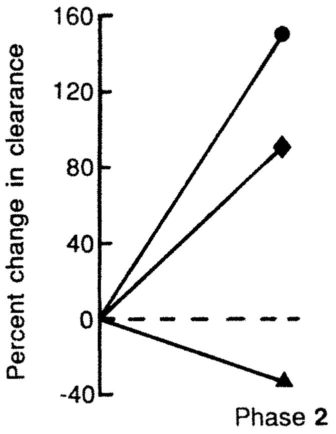

Figure 2. The percentage change in placental clearance of bupivacaine (*circle*), meperidine (*diamond*), and antipyrine (*triangle*) from baseline (phase 1) during umbilical perfusion with acidic Krebs' buffer (phase 2).

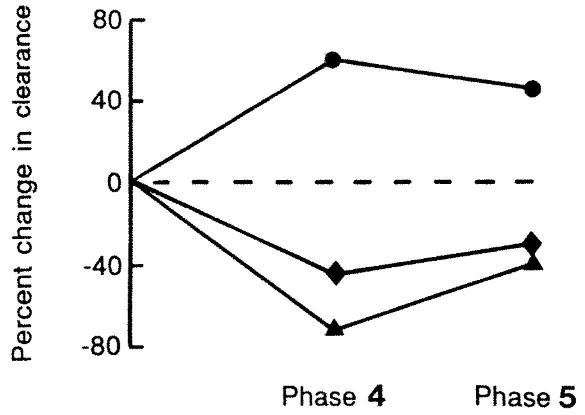

Figure 3. The percentage change in placental clearance of bupivacaine (*circles*), meperidine (*diamonds*), and antipyrine (*triangles*) during maternal hypotension induced by hypovolemia (phase 4) and after restoration of maternal blood volume (phase 5).

the transplacental gradient of binding protein (14) and pH (15–17) by virtue of ion-trapping. Clearance rates of local anesthetics and of meperidine have also been shown to be affected by the gradient of the binding protein, α_1-acid glycoprotein (10), but fetal concentrations of α_1-acid glycoprotein are very variable (26), and in vivo this variation may mask the ion-trapping effect. Using the present model, with the exclusion of protein on the fetal side, it has been possible to show that fetal acidosis may increase not only the equilibrium F/M ratio but also the rate of transfer of bupivacaine, and it is of interest to note that the same phenomenon has been observed, although to a lesser extent, with meperidine (Figure 2). At equilibrium the F/M plasma ratio for meperidine would be expected to increase more than that of bupivacaine in the presence of fetal acidosis, as the pK_a of the former drug is higher (3). However, meperidine is less lipophylic than bupivacaine, which may limit the increase in transfer that is possible in a single circuit of the placenta. These results suggest, however, that fetal acidosis may result in a fairly rapid rise in the concentration of both these basic drugs in fetal plasma. Because meperidine is more likely than bupivacaine to produce dose-related neonatal depression, the fact that this effect may be exacerbated in an acidotic baby is of potential clinical importance.

Antipyrine, being essentially nonionized and non-protein-bound, diffuses evenly throughout the total body water. In placental perfusion experiments it has been found a useful index of the integrity of the diffusional exchange mechanism (9). That antipyrine clearance in this study did not rise during phase 2 confirms that the changes in clearance of bupivacaine and meperidine resulted from the reduction in umbilical perfusate pH rather than from any vagary in placental function.

Placental clearance rates of local anesthetics, meperidine, and fentanyl have previously been shown to be markedly dependent on umbilical flow, whereas the clearance of antipyrine tends to plateau at higher umbilical flows (9–11). This may be because permeability begins to limit the transfer of the less lipophylic antipyrine at high umbilical flow. The effect of maternal placental flow is harder to evaluate. Maternal placental blood flow in the rabbit is difficult to measure directly. The uterine arteries are too small to permit electromagnetic measurement of flow, and microsphere techniques allow only a maximum of three isolated measurements of placental flow to be made retrospectively. If, however, umbilical flow is constant and the fetal-maternal exchange area remains intact, then the clearance of antipyrine can be expected to reflect maternal placental blood flow.

The observed decrease in antipyrine clearance in phase 4 therefore indicated that maternal flow was reduced by hemorrhage. It is of interest to note, moreover, that normal placental exchange did not appear to be restored completely by retransfusion. Meperidine transfer was also significantly reduced, and did not recover completely on retransfusion, indicating its dependence on maternal placental blood flow. Bupivacaine transfer was, if anything, increased by hypotension. An increase in bupivacaine transfer in association with apparently deteriorating placental exchange has been observed elsewhere (27), when there was a negative correlation between bupivacaine and antipyrine clearance. That bupivacaine clearance does not fall with reduced maternal flow is probably related to its high maternal protein binding and lipid solubility. There is thus a large maternal store of bupivacaine to draw on, and its lipophilicity ensures rapid equilibration.

Thus, in the presence of fetal acidosis, transfer to the fetus of basic drugs such as meperidine and bupivacaine may actually be enhanced. When there is maternal placental underperfusion, although the transfer of meperidine falls, that of bupivacaine may not be reduced. In view of the time scale of administration of these drugs in labor, the effect of fetal acidosis is likely to be more important clinically than maternal placental underperfusion, which will be transient as it affects only transfer rate and not the ultimate equilibrium ratio. If these results can be extrapolated to the clinical situation, then it is clear that a sick fetus will not escape the effects of basic drugs in the maternal circulation. This is important because the effect of meperidine particularly may exacerbate a poor neonatal status, and it represents an essentially reversible component of neonatal depression.

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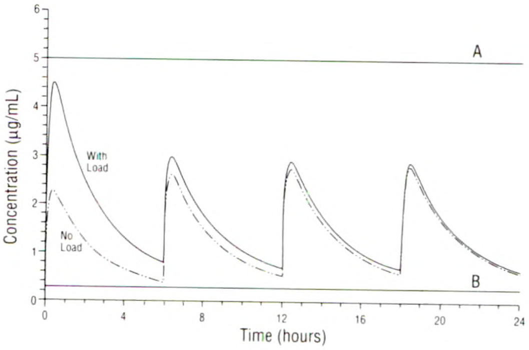

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Brief Summary
TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP, and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 µg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 µg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the in vivo mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery. **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. **Pediatric Use:** TORADOL is not recommended for use in children. **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. **Incidence greater than 1%:** Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%-9%. Reactions occurring in less than 3% are unmarked. **Incidence 1% or less:** Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. In vitro, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses >100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others.

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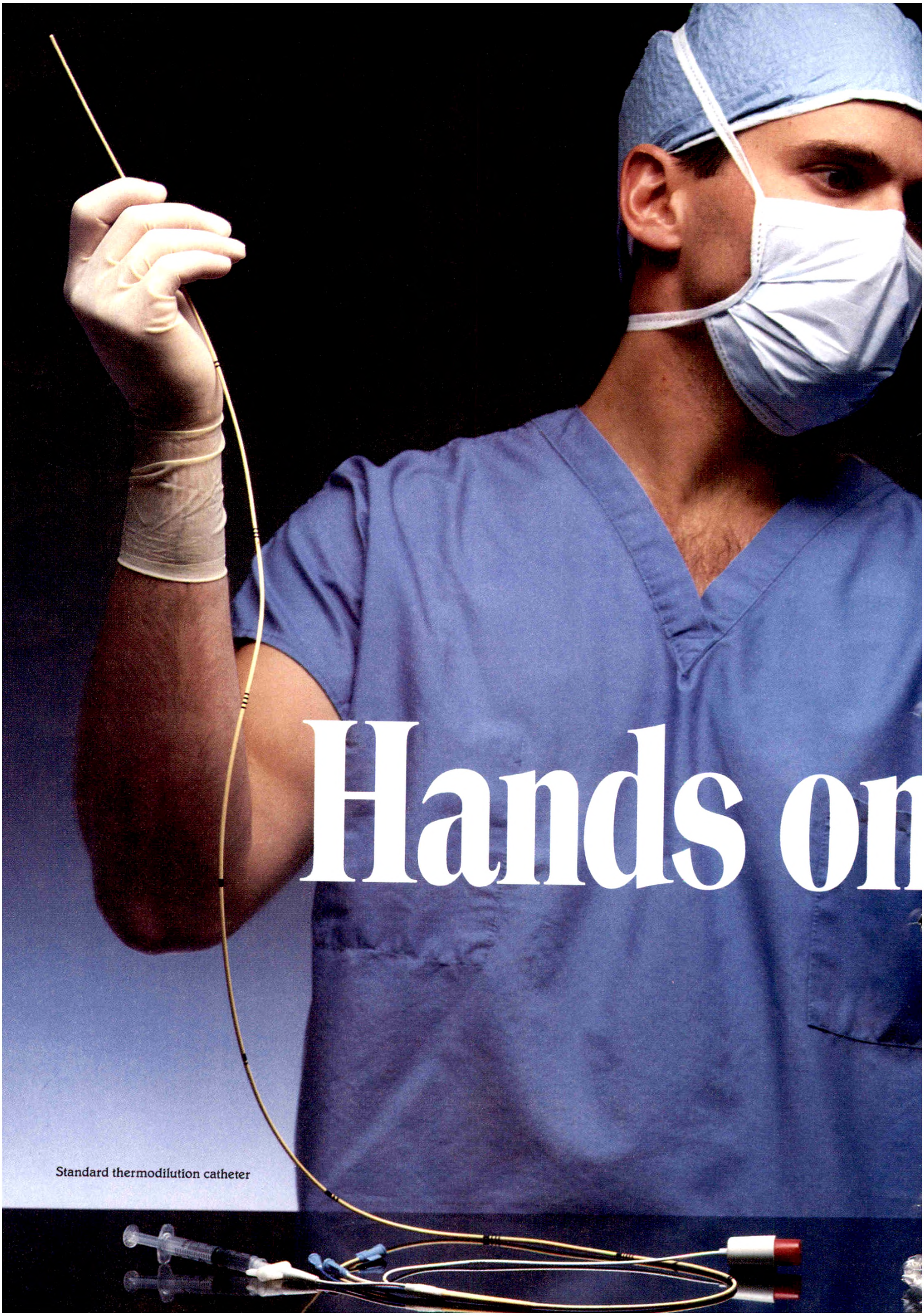

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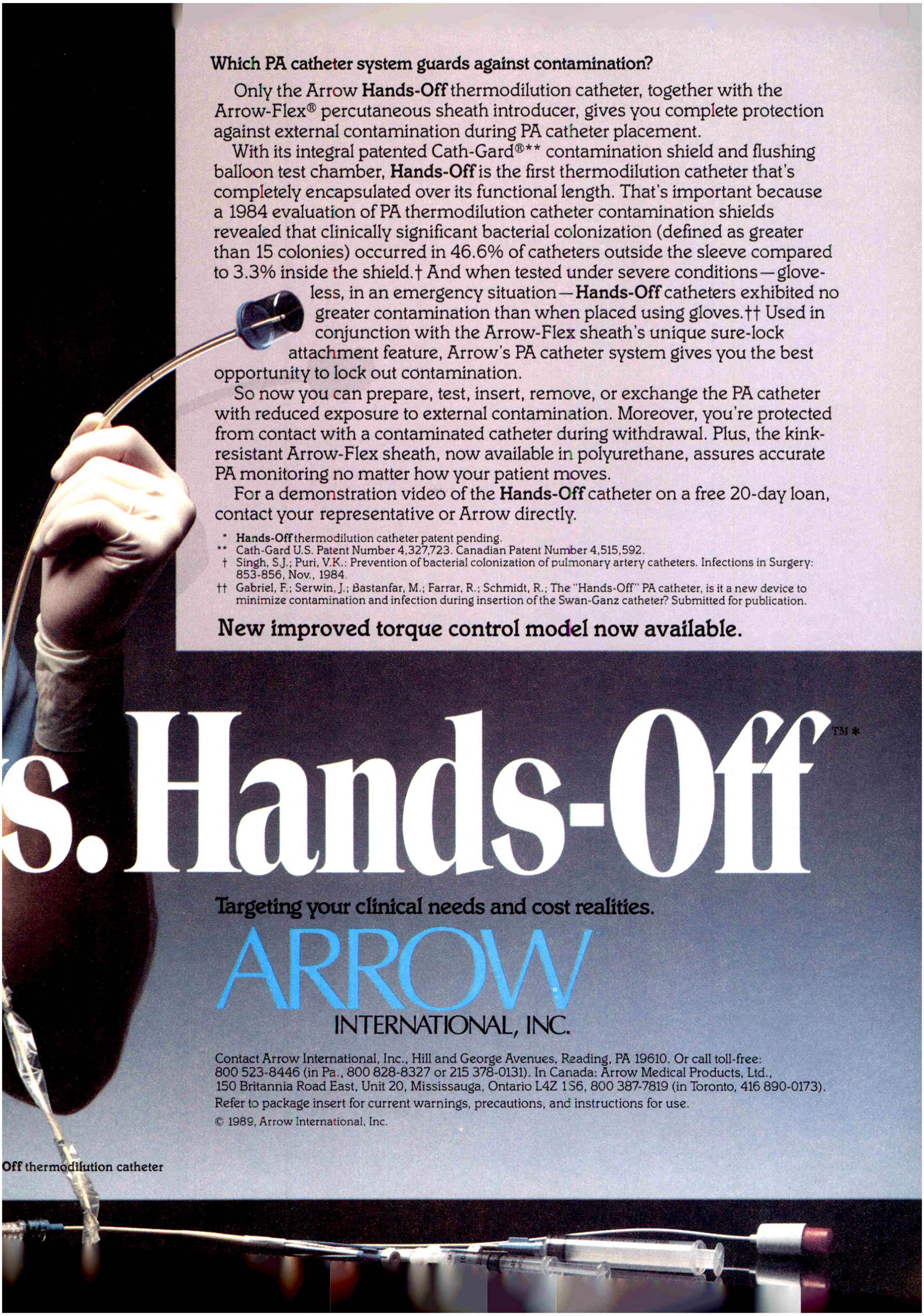

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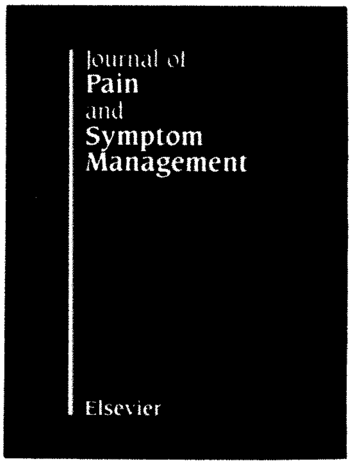

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Effect of Propofol on Cerebral Circulation and Autoregulation in the Baboon

Jan Van Hemelrijck, MD, William Fitch, MD, PhD, FFARCS, Maria Mattheussen, MD, Hugo Van Aken, MD, PhD, Chris Plets, MD, PhD, and Thierry Lauwers, MD

VAN HEMELRIJCK J, FITCH W, MATTHEUSSEN M, VAN AKEN H, PLETS C, LAUWERS T. Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesth Analg 1990;71:49–54.

The purpose of this study was to investigate the effect of propofol on cerebral blood flow, cerebral metabolism, and cerebrovascular autoregulatory capability. Seven anesthetized baboons were given propofol at three different infusion rates. An infusion of 3 mg·kg^{-1}·h^{-1} caused minimal changes, but infusion rates of 6 and 12 mg·kg^{-1}·h^{-1} decreased cerebral blood flow by 28% and 39%, respectively. The changes in cerebral metabolic rate of oxygen were not statistically significant. However, with the two higher infusion rates, there was a trend toward decrease, by 5% and 22%, respectively, for the cerebral metabolic rate of oxygen, and by 18% and 36% for the cerebral metabolic rate of glucose. A 25–30 mm Hg increase in arterial blood pressure had no influence on cerebral blood flow. Replacement of nitrous oxide by nitrogen had no significant influence on cerebral blood flow or metabolism.

It is concluded that propofol causes a dose-dependent decrease in cerebral blood flow. However, the study does not prove that this decrease in cerebral blood flow is accompanied by the same degree of decrease in cerebral metabolism. Further studies are clearly needed to clarify propofol's influence on the coupling between cerebral metabolism and blood flow. The physiologic responsiveness of the cerebral circulation to alterations in arterial pressure is well preserved. Propofol appears to prevent the metabolic stimulation and increased cerebral blood flow that has been associated with the administration of nitrous oxide.

Key Words: ANESTHETICS, INTRAVENOUS—propofol. BRAIN, BLOOD FLOW—propofol.

The use of nitrous oxide (N_2O) and volatile anesthetics in neuroanesthesia has been questioned because of their effects on cerebral circulation and metabolism. The availability of a total intravenous anesthetic technique that could provide a predictable depth of anesthesia and a rapid postoperative recovery would be a useful alternative to conventional inhalation techniques. Ideally, the coupling of cerebral blood flow and metabolism and the autoregulation of the cerebral circulation should not be affected by the anesthetic.

The pharmacokinetic properties of propofol make the drug suitable for maintenance of anesthesia by intravenous infusion (1). Propofol decreases both cerebral metabolism and cerebral blood flow (2,3), whereas CO_2 reactivity is preserved (3). However, the effect of propofol on cerebrovascular autoregulation has not been systematically studied.

The present study was undertaken to evaluate the effect of different infusion rates of propofol on cerebral metabolism and circulation and on circulatory autoregulation in the baboon. In addition, the effect of N_2O on cerebral blood flow, metabolism, and intracranial pressure during propofol infusions was investigated.

Methods

This study protocol was approved by the authors' institutional animal investigation committee, and the experiments were performed according to our institution's standards for laboratory animal care. Seven

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young adult baboons (12–17 kg) were anesthetized with 7.5 mg/kg IV thiopental after tranquilization with 1 mg/kg IM phencyclidine. Anesthesia was subsequently maintained with 70% N_2O in oxygen (O_2) supplemented with 2 mg IM phencyclidine and 100 mg IM succinylcholine every 30 min (4). The trachea was intubated and ventilation was controlled (Sulla Ventilator, Dräger) to maintain CO_2 tension between 38 and 42 mm Hg as assessed by the continuous measurement of end-tidal CO_2 concentration (Nelcor N 1000) and intermittent blood gas analysis (ABL II). Correction was made, where necessary, for any temperature difference between the animal and the electrode system of the blood gas analyzer.

A catheter was inserted into the femoral artery for direct measurement of the arterial pressure. A balloon-tipped flow-directed pulmonary artery thermodilution catheter (5F gauge, Edwards Laboratories) was introduced through the femoral vein to the pulmonary artery for measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output using a thermodilution technique (Cardiac Output Computer, Edwards Laboratories). Additional catheters were introduced into the contralateral femoral vein for administration of fluids (3 $mL \cdot kg^{-1} \cdot h^{-1}$, saline and Ringer's lactate) and into an arm vein for administration of propofol. A catheter was introduced in the lateral ventricle through a burr hole for continuous measurement of intracranial pressure.

Systemic arterial, right atrial, pulmonary arterial, sagittal sinus venous, and intracranial pressures were continuously monitored (Gould Statham Transducer, Heilige). All pressures were zero-referenced to the external auditory meatus. Mean arterial pressure (MAP), mean right atrial pressure, mean pulmonary artery pressure, intracranial pressure (ICP), and sagittal sinus venous pressure were calculated by electronic integration of the transducer signal. The electrocardiogram was continuously monitored. Body temperature was measured from the thermistor of the thermodilution catheter and maintained within normal limits (36°–38°C) using heating lamps.

To measure cerebral blood flow (CBF), xenon 133 was injected in the right internal carotid artery through the linguofacial trunk after all other branches of the external carotid artery had been ligated distally. After removal of the parietal muscles, CBF was determined from the height/area equation by monitoring the peak count and the rate of clearance by external scintillation counting over the right parietal area (5).

Arterial and cerebral venous oxygen contents (ABL II) and glucose concentrations were measured simultaneously, and cerebral metabolic rates for oxygen ($CMRo_2$) and glucose (CMR_{gluc}) were calculated as follows: $CMRo_2 = CBF \times (Cao_2 - Cvo_2)$ and $CMR_{gluc} = CBF \times$ arteriovenous glucose concentration difference.

After the determination of baseline values—i.e., under 70% N_2O in O_2 and phencyclidine—an intravenous loading dose of 1 mg/kg propofol was given and an intravenous infusion of the drug at a rate of 3 $mg \cdot kg^{-1} \cdot h^{-1}$ was started for 30 min before all measurements were obtained using this dose of propofol. Subsequently, the infusion rate was increased to 6 $mg \cdot kg^{-1} \cdot h^{-1}$ for 30 min; again, all necessary measurements were obtained while using this dose and the dose of 12 $mg \cdot kg^{-1} \cdot h^{-1}$. The effects of the infusions of propofol were investigated in association with the administration of N_2O or nitrogen in 30% O_2—the sequence of the administrations of the N_2O/air being randomized. Measurements of the variables of interest were obtained with each infusion rate of propofol and in relation to the withdrawal/addition of N_2O.

During each measurement, CBF and cardiac output were determined, the relevant hemodynamic variables recorded, and the appropriate samples of arterial and cerebral venous blood obtained.

The physiologic responsiveness of the cerebral circulation was assessed by noting the changes (if any) in CBF, produced by an acute increase in MAP of approximately 25 mm Hg (induced by the intravenous administration of angiotensin II amide [Ciba]), at baseline (after control measurements were obtained) and during the continuous infusion of propofol at dose rates of 3, 6, and 12 $mg \cdot kg^{-1} \cdot h^{-1}$.

As time constraints did not allow establishment of steady-state blood concentrations, the mean blood propofol level with each infusion rate was calculated as the mean of the levels 30 min after the start and at the middle and end of each infusion period.

Mean values and standard deviation were calculated for each variable. Statistical analysis was performed using the Friedman test and the Wilcoxon signed-rank test for differences between control measurements and measurements at the three infusion rates. The Wilcoxon signed-rank test was used to detect any statistically significant change in CBF during the autoregulation test, $P < 0.05$ being considered significant.

Results

The propofol blood level at an infusion rate of 3 $mg \cdot kg^{-1} \cdot h^{-1}$ was 0.6 ± 0.07 μg/mL (mean ± SD). The

Table 1. Hemodynamic Values Before and During Propofol at Three Infusion Rates With and Without N_2O in Baboons ($n = 7$)

	Control with N_2O	Propofol, 3 mg·kg^{-1}·h^{-1}		Propofol, 6 mg·kg^{-1}·h^{-1}		Propofol, 12 mg·kg^{-1}·h^{-1}	
		N_2O	Air	N_2O	Air	N_2O	Air
HR (beats/min)	103 ± 18.63	102 ± 24.09	110 ± 23.01	107 ± 19.61	116 ± 15.64	104 ± 13.53	118 ± 8.88
MAP (mm Hg)	109 ± 14.30	107 ± 16.85	107 ± 7.14	97 ± 9.32[a]	111 ± 17.26[b]	90 ± 12.87[a]	90 ± 12.87[a]
MPAP (mm Hg)	13.61 ± 2.58	13.40 ± 4.39	11.13 ± 1.93	12.43 ± 2.70	12.86 ± 2.27	13.14 ± 2.73	13.14 ± 2.04
CO (L/min)	2.63 ± 0.54	2.47 ± 0.45	2.40 ± 0.42	2.49 ± 0.45	2.55 ± 0.64	2.41 ± 0.36	2.51 ± 0.47
PCWP (mm Hg)	2.89 ± 1.29	2.40 ± 0.89	2.13 ± 1.44	2.57 ± 0.98	2.86 ± 0.9	2.43 ± 1.13	2.57 ± 1.13
SVR (dyne·s·cm^{-5})	3391 ± 730	3568 ± 905	3668 ± 708	3158 ± 466	3577 ± 679	3000 ± 552	3128 ± 657

All values are mean ± SD.

HR, heart rate; MAP, mean arterial pressure; MPAP, mean arterial pulmonary pressure; CO, cardiac output; PCWP, wedge pressure; SVR, systemic vascular resistance.

[a] $P < 0.05$ as compared with baseline.

[b] $P < 0.05$ as compared with N_2O at corresponding infusion rates.

Table 2. Cerebrovascular Variables Before and During Propofol Infusion at Three Rates With and Without N_2O in Baboons ($n = 7$)

	Control with N_2O	Propofol, 3 mg·kg^{-1}·h^{-1}		Propofol, 6 mg·kg^{-1}·h^{-1}		Propofol, 12 mg·kg^{-1}·h^{-1}	
		N_2O	Air	N_2O	Air	N_2O	Air
CBF (mL·min^{-1}·100 g^{-1})	50.01 ± 4.49	46.41 ± 6.52	44.53 ± 3.20	35.79 ± 6.07[a]	5.48 ± 5.16[a]	30.31 ± 7.56[a]	29.72 ± 7.69[a]
$CMRo_2$ (mL O_2·min^{-1}·100 g^{-1})	2.03 ± 0.44	2.20 ± 0.47	2.40 ± 0.34	1.93 ± 0.44	2.06 ± 0.42	1.57 ± 0.44	1.65 ± 0.40
CMR_{gluc} (mg·min^{-1}·100 g^{-1})	3.74 ± 0.67	4.13 ± 0.94	3.80 ± 1.17	3.03 ± 0.44	3.17 ± 0.96	2.38 ± 0.83	2.66 ± 0.40
ICP (mm Hg)	11.79 ± 2.64	13.00 ± 4.85	11.75 ± 4.19	12.57 ± 3.78	13.43 ± 3.74	14.43 ± 4.43	14.00 ± 3.27
SSVP (mm Hg)	10.25 ± 3.94	9.60 ± 2.07	9.25 ± 1.26	7.57 ± 2.76	8.57 ± 3.36	7.14 ± 4.30	7.14 ± 3.98

All values are mean ± SD.

CBF, cerebral blood flow; $CMRo_2$, cerebral metabolic rate of oxygen; CMR_{gluc}, cerebral metabolic rate of glucose; ICP, intracranial pressure; SSVP, superior sagittal sinus pressure.

[a] $P < 0.05$ as compared with control.

blood level reached 1.42 ± 46 μg/mL at an infusion rate of 6 mg·kg^{-1}·h^{-1}and 2.86 ± 1.01 μg/mL at a rate of 12 mg·kg^{-1}·h^{-1}.

Hemodynamic changes during the three different propofol infusion rates are summarized in Table 1. A significant decrease in MAP occurred at infusion rates of 6 and 12 mg·kg^{-1}·h^{-1} with N_2O ($P < 0.05$). Mean arterial pressure is significantly higher with air-O_2 ventilation than with N_2O/O_2 for the 6- and 12-mg·kg^{-1}·h^{-1} infusion rates. Changes in heart rate, pulmonary artery pressures, left atrium filling pressure, and cardiac output were not significant.

Cerebrovascular variables are summarized in Table 2. Cerebral blood flow decreased significantly ($P < 0.05$) from 50. ± 4.5 to 46.4 ± 6.5 mL·min^{-1}·100 g^{-1} at an infusion rate of 3 mg·kg^{-1}·h^{-1} with N_2O. At propofol infusions of 6 and 12 mg·kg^{-1}·h^{-1} with N_2O CBF decreased significantly to 35.8 ± 6.1 and 30.3 ± 7.6 mL/min, respectively. There was no significant difference between the CBF with air/O_2 or N_2O/O_2 ventilation at each propofol infusion rate.

There were no significant changes in ICP or sagittal sinus venous pressure with the different infusion rates. They were not influenced by the presence of N_2O.

Although the numerical averages of $CMRo_2$ and CMR_{gluc} decreased with the two higher propofol infusion rates, these decreases were not statistically significant. The metabolic rate was not altered by N_2O.

Figure 1 shows the change in CBF during an acute increase in mean arterial pressure of about 25 mm Hg before the administration of propofol and during the continuous infusion of 3, 6, and 12 mg·kg^{-1}·h^{-1} propofol. Because CBF did not differ significantly from its baseline value when MAP was increased acutely either before the administration of propofol or during the three different infusion rates of propofol, it can be assumed that the cerebral vessels were responding in a normal physiologic manner to the acute alterations in systemic arterial pressure.

Discussion

The time taken for propofol to reach a stable blood concentration when administered as a fixed-rate infusion exceeds 1 h (6). Steady-state blood concentrations were, therefore, not reached in this study when each measurement sequence was begun. For this

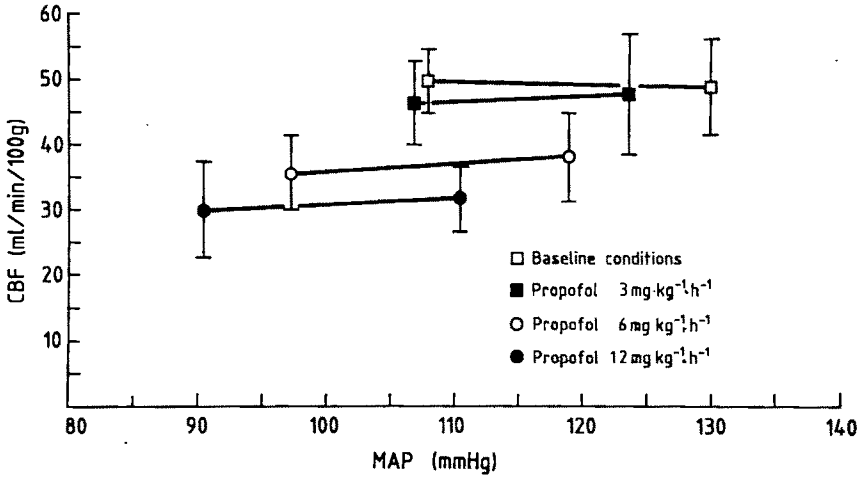

Figure 1. Cerebral blood flow (CBF) before and during acute increases in systemic arterial pressure. Cerebral blood flow was measured before and during an acute increase in MAP produced by intravenous infusion of angiotensin II amide in the absence of propofol and during infusion of propofol at rates of 3, 6, and 12 $mg \cdot kg^{-1} \cdot h^{-1}$.

reason, the propofol blood concentration for each infusion rate was calculated as the mean of three measurements.

The mean propofol blood level at an infusion rate of 3 $mg \cdot kg^{-1} \cdot h^{-1}$ was only 0.6 ± 0.07 μg/mL. Because patients are awake after a propofol infusion when the blood concentration decreases below 1.1 μg/mL (1), effects at this drug level are probably of little if any clinical relevance. The blood propofol concentrations during the infusions at 6 and 12 $mg \cdot kg^{-1} \cdot h^{-1}$ were 1.42 ± 0.46 and 2.86 ± 1.01 μg/mL, respectively. A concentration of 2.97 ± 1 μg/mL has been described as being adequate for nonmajor surgery when N_2O and meperidine are also used (1). Similar values have been determined for propofol infusions supplementing 67% N_2O in patients premedicated with lorazepam or morphine (7,8). A concentration of 2.5 or 3 μg/mL was aimed for, with a computer-assisted infusion technique of total intravenous anesthesia (9,10).

Cardiovascular variables remained remarkably stable throughout this study, with a maximal decrease in MAP of 17% at a propofol infusion rate of 12 $mg \cdot kg^{-1} \cdot h^{-1}$. The decrease in MAP can partly be explained by an 11% decrease in systemic vascular resistance. Cardiac output, pulmonary artery pressures, pulmonary capillary wedge pressure, and heart rate (for the combination with N_2O) did not change significantly. The changes in circulatory variables are in agreement with other studies on propofol infusions in healthy subjects (11–13). The absence of an increase in heart rate in response to a decrease in blood pressure during propofol infusions has been ascribed to a central sympatholytic and/or vagotonic mechanism (14). An increase in MAP and systemic vascular resistance with air/O_2 as compared with N_2O/O_2 ventilation for the 6- and 12-$mg \cdot kg^{-1} \cdot h^{-1}$ infusion rates can probably be explained by an increase in sympathetic activity, due to lighter planes of anesthesia. In none of the animals was blood pressure out of the presumed cerebrovascular autoregulatory limits at any time.

A decrease in ICP has been described with 1 mg/kg IV propofol in patients with intracerebral injuries (15). A decrease in CBF and hence in cerebral blood volume can significantly diminish ICP when cerebral compliance is reduced; however, with normal cerebral compliance, changes in CBF have little influence on ICP.

A reduction in CBF proportional to the propofol infusion rate was observed. Although this reduction was minimal during the 3-$mg \cdot kg^{-1} \cdot h^{-1}$ infusion, the 6- and 12-$mg \cdot kg^{-1} \cdot h^{-1}$ infusion rates resulted in reductions of 28% and 39%, respectively. A reduction in CBF of 51% has been reported in coronary artery bypass patients with an infusion rate of 12 $mg \cdot kg^{-1} \cdot h^{-1}$ (3). Presumably, the difference in degree of CBF reduction can be explained by a different anesthetic background and by eventually differing blood concentrations (not measured in the human study), as well as species differences. A 27.6% reduction in CBF was described in humans given a propofol infusion designed to produce a stable blood concentration of 4 μg/mL with N_2O and 0.5% enflurane as background anesthetics (2). The smaller decrease in CBF in spite of the higher expected blood levels can probably be partly assigned to the background anesthetic, as enflurane causes a reduction in cerebral vascular resistance (16) and could thereby modify the CBF-lowering effect of propofol.

The cerebral metabolic rates for oxygen and glucose did not change significantly with the 6- and 12-$mg \cdot kg^{-1} \cdot h^{-1}$ infusion rates, although the numerical means decreased by 5% and 22%, and 18% and

36%, respectively. Apparently, the decrease in CBF caused by propofol is incompletely coupled to a comparable decrease in cerebral metabolism. This raises concern that propofol may decrease CBF more than O_2 demand. However, one animal had an unexplained abnormally low cerebral metabolic rate ($CMRo_2$ 1.41 mL $O_2 \cdot min^{-1} \cdot 100\ g^{-1}$; CMR_{gluc} 2.65 $mg \cdot min^{-1} \cdot 100\ g^{-1}$) with a normal CBF (58.94 $mL \cdot min^{-1} \cdot 100\ g^{-1}$) under baseline conditions. Its cerebral metabolism increased during the experiment. Omitting the data on cerebral metabolism of this study animal results in a significant decrease in $CMRo_2$ of 15% and 36%, and a significant decrease of CMR_{gluc} of 20% and 44% for the 6- and 12-$mL \cdot kg^{-1} \cdot h^{-1}$ infusion rates, respectively. Second, we acknowledge a potential error introduced by our calculation of $CMRo_2$ and CMR_{gluc}. This calculation assumes that CBF in the region under the scintillation detector changes uniformly in response to propofol as does the arteriosagittal sinus oxygen content difference. However, regional differences may exist, and the method of measuring CBF may overestimate propofol's influence on global CBF. A 36% reduction in $CMRo_2$ was measured in patients before coronary artery surgery, during a propofol infusion of 12 $mg \cdot kg^{-1} \cdot h^{-1}$ (3).

In spite of the fact that N_2O increases $CMRo_2$ and CBF (17,18), we were unable to detect any significant changes in cerebral metabolism or CBF when N_2O was discontinued during the three propofol infusions. These data suggest that propofol obtunds the metabolic activation and subsequent increase in CBF which may be associated with the administration of N_2O. In contrast, a 10% increase in CBF has been described in the rabbit when N_2O was added to a pentobarbital-fentanyl anesthetic (19). Nevertheless, the cerebral metabolic stimulating effects of N_2O can be blocked by sufficient levels of background anesthesia (17,20).

Cerebral blood flow did not change significantly when MAP was increased acutely either before or during the administration of propofol at three different propofol infusion rates. The cerebral vessels were reacting physiologically to the imposed pressure change; propofol thus leaves the cerebrovascular autoregulatory responses to increasing MAP unaltered. Angiotensin II itself, used to provoke the blood pressure increases, has no effect on CBF unless administered immediately adjacent to a cerebral vessel (21,22). The same autoregulation test, under similar background anesthetic conditions, is capable of detecting disturbed autoregulation with high concentrations of isoflurane and during adenosine triphosphate-induced hypotension (23,24).

The basic anesthetic technique used in this study, namely phencyclidine, N_2O, and succinylcholine, has been previously used for studies on cerebral circulatory effects of drugs, including autoregulation testing (4,23–25). Because N_2O, succinylcholine, and phencyclidine were given during the entire experiment, we cannot exclude some influence of these agents on systemic and cerebrovascular hemodynamics. However, because all measurements were made under similar anesthetic background conditions, it seems likely that the observed changes can be ascribed to propofol.

Because phencyclidine alone cannot be considered as a full anesthetic, it would be unethical to perform surgery on the animals without the addition of N_2O. For the same reason, baseline measurements were performed including N_2O in the background anesthetic. The effect of propofol on autoregulation was also tested under the same anesthetic conditions, including N_2O. When propofol completed the basic anesthetic, it was possible to study the effect of the abolition of N_2O.

In conclusion, a dose-related decrease in CBF was found during propofol infusions in baboons. However, partly due to the small number of animals studied, the study failed to demonstrate unequivocally a proportional decrease in cerebral metabolism. The autoregulatory response to blood pressure changes was not impaired by propofol. The stimulatory effects of N_2O on cerebral metabolism were obtunded by propofol.

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1990;71:55–9

Effect of *d*-Tubocurarine Pretreatment on Succinylcholine Twitch Augmentation and Neuromuscular Blockade

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SZALADOS JE, DONATI F, BEVAN DR. Effect of *d*-tubocurarine pretreatment on succinylcholine twitch augmentation and neuromuscular blockade. Anesth Analg 1990;71:55–9.

Subparalyzing doses of d-tubocurarine (dTC) given before succinylcholine decrease the duration of neuromuscular blockade. In animal preparations, they also abolish succinylcholine-induced twitch augmentation, defined as a greater-than-maximal contraction in response to a single stimulus. To determine quantitatively the effect of dTC on succinylcholine potency and on twitch augmentation in humans, 60 adult patients, ASA physical status I or II, were assigned randomly to receive either 0.05 mg/kg of dTC or saline 2 min before induction of anesthesia with fentanyl and thiopental. Train-of-four stimulation was applied every 12 s to the ulnar nerve and the force of contraction of the adductor pollicis muscle was measured. One minute after induction of anesthesia, 0.15, 0.20, 0.25, 0.35, or 0.50 mg/kg of succinylcholine was given. The height of the first twitch (T1) reached 121% ± 6% (mean ± SEM) of control without dTC, and was virtually abolished by dTC pretreatment (105% ± 1%, $P < 0.01$). Twitch augmentation was more noticeable with lower doses of succinylcholine, and was not observed in the response to the fourth stimulus of the train of four (T4). The potency of succinylcholine was decreased by approximately one-half in the dTC-pretreated groups. The ED_{50} was 0.27 ± 0.04 mg/kg without dTC and 0.50 ± 0.06 mg/kg with dTC ($P < 0.002$). The corresponding values for ED_{90} were 0.51 ± 0.07 and 1.02 ± 0.12 mg/kg, respectively ($P < 0.02$). The ED_{95} values were 0.63 ± 0.09 and 1.28 ± 0.15 mg/kg, respectively ($P < 0.02$). The slopes of the regression lines did not deviate significantly from parallelism. It is concluded that dTC, 0.05 mg/kg, given 3 min before succinylcholine, decreases the potency of succinylcholine by almost 50% and abolishes succinylcholine-associated twitch augmentation.

Key Words: INTERACTIONS (DRUG), *d*-TUBOCURARINE, SUCCINYLCHOLINE. NEUROMUSCULAR RELAXANTS, *d*-TUBOCURARINE, SUCCINYLCHOLINE.

Subparalyzing doses of *d*-tubocurarine (dTC) are often administered before succinylcholine to prevent fasciculations. Such pretreatment has been reported to increase the onset time of neuromuscular blockade and shorten its duration (1–4). In animal preparations, succinylcholine has been demonstrated to produce twitch augmentation, which is a greater-than-maximal contraction in response to a single stimulus applied to the nerve (5,6). This effect is abolished by small doses of dTC (6) or vecuronium (7). Simultaneous recordings from the muscle and the ventral root suggest that this action of nondepolarizing relaxants is presynaptic (6,7).

It is generally recommended that the dose of succinylcholine be increased after the administration of dTC. This is based on the finding that dTC pretreatment decreases the duration of succinylcholine blockade (1), and not on potency determinations for succinylcholine. Twitch augmentation has been reported in humans (8–10), but the dose-effect relationship has not been studied. Furthermore, the effect of subparalyzing doses of dTC has not been investigated. Obtaining this information would be useful, as twitch augmentation and fasciculations probably have a common mechanism of action (6).

Therefore, the purpose of this study was threefold: (a) to compare dose-response data for succinylcholine alone and after pretreatment with a subparalyzing dose of dTC, (b) to determine the effects of different succinylcholine doses on twitch augmentation, and (c) to study the effects of dTC on twitch augmentation.

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Methods

The protocol was approved by the Hospital Ethics Committee. Sixty adult patients, ASA physical status I or II, who were scheduled for elective surgery were included in the study after appropriate consent had been obtained. Patients with known or suspected hepatic, renal, or neuromuscular disorders were excluded, as were patients with electrolyte abnormalities or those taking medications known or suspected to interfere with neuromuscular function. Patients with a personal or family history of succinylcholine apnea or malignant hyperthermia were also excluded. Premedication was at the discretion of the anesthesiologist.

In the operating room, electrocardiogram and pulse oximetry were monitored continuously. Blood pressure was measured noninvasively with a cuff attached to the arm not involved with neuromuscular monitoring. Before induction of anesthesia, the hand and forearm were immobilized in a splint and surface electrodes were placed over the ulnar nerve at the elbow. The force of contraction of the adductor pollicis muscle was measured using a Grass FT-10 force transducer and recorded on paper.

Patients were randomly assigned to receive dTC (0.05 mg/kg intravenously) or saline 2 min before induction of anesthesia with 3–5 mg/kg of thiopental and 1–2 μg/kg of fentanyl. After loss of consciousness, the patients' lungs were ventilated manually via a mask, using oxygen and nitrous oxide (up to 60% inspired) as required to maintain anesthesia. No halogenated inhalation anesthetic agents were administered during the study period. After induction, supramaximal train-of-four stimulation (2 Hz for 2 s) was applied, and repeated every 12 s. One minute after induction (3 min after the injection of dTC in the patients who received the drug), 0.15, 0.20, 0.25, 0.35, or 0.50 mg/kg of succinylcholine was administered by rapid intravenous bolus. The dose was selected at random, and six patients received each dose. Neuromuscular recording was continued until maximum twitch depression was identified and evidence of early recovery was present. At this time, an additional dose of succinylcholine or a nondepolarizing relaxant was administered to facilitate tracheal intubation. The remainder of the anesthetic management was left to the discretion of the anesthesiologist.

A few seconds after succinylcholine injection, the response to train-of-four stimulation typically showed twitch augmentation, which was most apparent on the first response (T1) and virtually absent from the fourth (T4) (10) (Figure 1). Then muscular blockade became manifest, and T4 was depressed to a greater extent than T1, possibly because twitch augmentation of T1 persists as blockade develops. Twitch augmentation was defined as the largest T1 twitch height compared with T1 control.

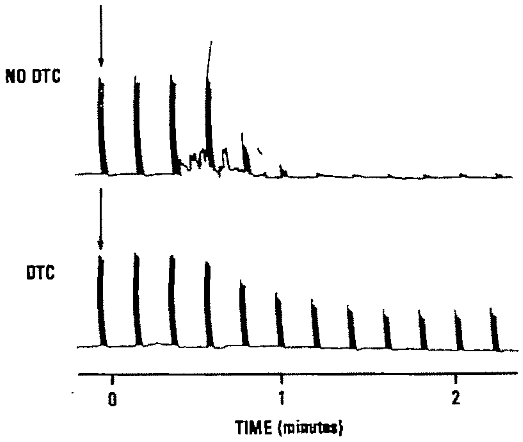

Figure 1. Representative tracing. Succinylcholine, 0.5 mg/kg, was given at the *arrow*. The normal response included twitch augmentation (a T1 greater than normal). This occurred at the same time as fasciculations (changing baseline) and was followed by neuromuscular blockade. With 0.05 mg/kg of dTC, administered 3 min earlier (*bottom panel*), no block was seen before succinylcholine was given. No twitch augmentation and no fasciculations were seen after 0.5 mg/kg of succinylcholine (*arrow*). Neuromuscular blockade was less than in the previous example.

Neuromuscular blockade was defined as depression of T4 expressed as a percentage of control T4. This measurement was chosen to avoid the contribution of any twitch augmentation, which is more apparent on T1 than T4 (11). Onset time of twitch augmentation was defined as the interval between injection of succinylcholine until maximum T1. Onset of neuromuscular blockade was the interval between administration of succinylcholine until maximum T4 depression. Dose-response relationships were calculated from linear regressions of the logit transformation of twitch depressions and the logarithm of succinylcholine doses (12). These regression lines were used to obtain the ED_{50}, ED_{90}, and ED_{95}. The standard error of the estimate for the mean (SEM) was used as an index of dispersion (13). Onset values are presented as mean ± SEM. Statistical comparisons between dTC-treated and untreated groups were done using the unpaired Student's *t*-test, and the level of significance was set at $P < 0.05$.

Results

There were 16 men and 44 women in this study. The demographic data are summarized in Table 1. There were no significant differences between the groups.

Table 1. Demographic Data

	dTC	No dTC	Total
Sex (M/F)	6/24	10/20	16/44
Age (yr)[a]	39 ± 3	46 ± 3	49 ± 2
Weight (kg)[a]	55 ± 3	60 ± 3	66 ± 2

[a] Mean ± SEM.

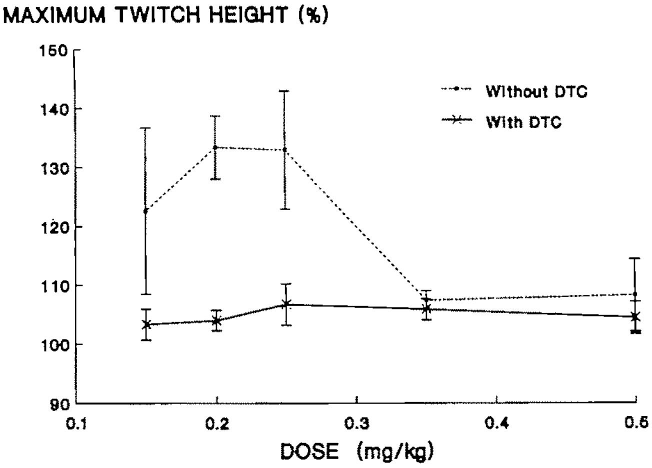

Figure 2. Maximum T1 (a measure of twitch augmentation), expressed as percent of control, as a function of the dose of succinylcholine given.

The mean time to maximum neuromuscular blockade was 102 ± 7 s (SEM) in groups pretreated with dTC and 121 ± 8 s without dTC (P = NS). Twitch augmentation occurred in all but two of 30 patients who did not receive dTC, and the magnitude of this effect was more marked at lower doses of succinylcholine (Figure 2). Mean maximum T1 was 121% ± 6%. However, the patients who received dTC before succinylcholine had almost no twitch augmentation. The maximum T1 was 105% ± 1% of control ($P < 0.01$). The mean time from the administration of succinylcholine to maximum twitch augmentation was 53 ± 4.3 s. Twitch augmentation was not apparent on T4. The maximum height of T4 relative to T4 control was 102% ± 0.5% and 101% ± 0.4% in dTC-treated and untreated groups, respectively (P = NS).

The potency of succinylcholine was decreased by approximately one-half in patients who were pretreated with dTC (Figure 3). The ED_{50}, ED_{90}, and ED_{95} are listed in Table 2. The slopes of the regression lines did not deviate significantly from parallelism (4.16 ± 1.45 vs 3.89 ± 1.08 in saline- and dTC-treated groups, respectively). The ED_{50} was 1.81 ± 0.24 times as large with dTC. The 95% confidence limits were 1.56–2.08.

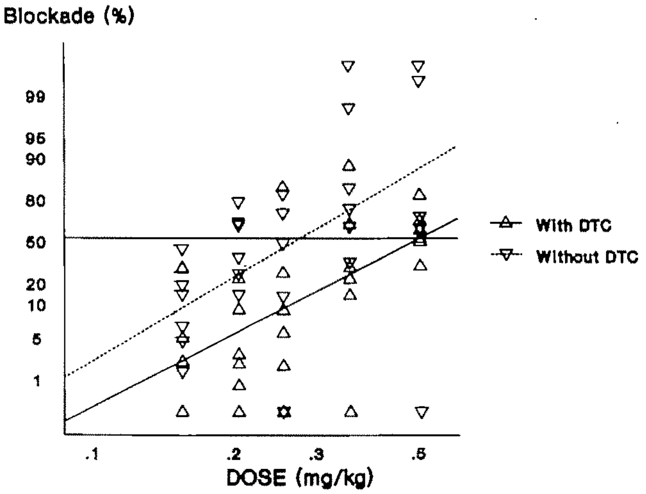

Figure 3. Dose-response curves for succinylcholine with and without dTC pretreatment (logit twitch depression vs log dose).

Table 2. Dose-Response Data for Succinylcholine With and Without *d*-Tubocurarine Pretreatment (mean ± SEM)

	No dTC (mg/kg)	dTC (mg/kg)
ED_{50}	0.27 ± 0.04	0.50 ± 0.06
ED_{90}	0.51 ± 0.07	1.02 ± 0.12
ED_{95}	0.63 ± 0.09	1.28 ± 0.15

Discussion

This study showed that a subparalyzing dose of dTC (0.05 mg/kg), when administered 3 min before succinylcholine, interacts with the latter drug in two ways. It reduces the potency of succinylcholine by approximately one-half, and it abolishes twitch augmentation.

In this study, the dose of dTC chosen (0.05 mg/kg) had been demonstrated to prevent succinylcholine-induced fasciculations (1,3,4). It was administered before the induction of anesthesia, and preceded succinylcholine by 3 min, a time interval that is effective in preventing fasciculations (1,3). One aspect of the methodology differs markedly from the clinical situation: the dose of succinylcholine was reduced. This was done because higher doses (1–2 mg/kg) abolish twitch height completely and dose-response curves cannot be obtained. However, succinylcholine was administered shortly after thiopental was injected. This was done to simulate the clinical situation as closely as possible and to avoid any possible interference from nitrous oxide, or any other agent used to maintain anesthesia, on succinylcholine potency or fasciculations. Thus, we did not wait for the baseline to stabilize. Probably only a small error was introduced by such a method because little change in baseline occurs during the 1–2 min required to observe the effects of succinylcholine. Furthermore, a small change in control twitch height does not affect measurements of profound neuromuscular blockade.

The doses chosen for this study were based on potency estimates obtained previously in the same institution (11), allowing for a 50% increase in succinylcholine requirement if dTC is used. This last figure was based on the common practice of administering 1.5 mg/kg of succinylcholine, instead of 1.0 mg/kg, if preceded by dTC (1,3). The ED_{50} and ED_{90} for succinylcholine alone were within the range of doses tested. However, the potency of succinylcholine was less than expected, and dTC had more antagonistic effect than anticipated. As a result, for succinylcholine preceded by dTC, only the ED_{50} was within the dose range tested. Thus, although the comparisons of the ED_{50} values are probably reliable, more error is likely to exist in the estimates of the ED_{90} and ED_{95} after dTC administration. However, the dose-response curves were parallel, indicating that the effect of dTC on succinylcholine is not only present in the 0.15–0.5-mg/kg dose range, but also and to a similar degree at higher doses (1–2 mg/kg).

Previous estimates of the potency of succinylcholine indicated ED_{50} and ED_{90} values lower than in this study. For example, Smith et al. reported an ED_{90} of 0.25–0.30 mg/kg (11). Cook et al. (14) calculated an ED_{90} of 0.20 mg/kg by extrapolating recovery data obtained by Walts and Dillon (15) and Katz and Ryan (16). Miller et al. (17) measured an ED_{90} of approximately 0.18 mg/kg under halothane anesthesia. In comparison, our results show the ED_{90} of succinylcholine to be 0.51 and the ED_{50} to be 0.27 mg/kg. Halothane might have potentiated neuromuscular blockade in two of these studies (14,18). However, Smith et al. (11) used no inhalational agent. The only methodological difference between the study of Smith et al. and the present investigation is the use of nitrous oxide for the maintenance of anesthesia and during stabilization of baseline. In the present study, maximum neuromuscular blockade occurred 2–3 min after induction of anesthesia, at a time when nitrous oxide, if and when given, did not have time to redistribute to muscle. This raises the possibility of an interaction between nitrous oxide and succinylcholine. This hypothesis appears to be supported by the recent results of Chestnut et al. (18), who determined the potency of succinylcholine given shortly after the induction agent. The ED_{50} was 0.31 mg/kg, and the ED_{95} was 0.51 mg/kg, similar to our findings of 0.27 and 0.63 mg/kg, respectively.

Twitch augmentation has been reported in animal studies after administration of succinylcholine (5–7). This phenomenon is abolished by dTC (6). Recordings of action potentials propagated in a retrograde fashion to the anterior ramus of the cat suggest that the mechanism of action of fasciculations is presynaptic, and that dTC interferes with this mechanism, possibly through a receptor. Twitch augmentation has also been reported in humans (8–10), and the present study demonstrates that the phenomenon can be abolished by a subparalyzing dose of dTC. This suggests that twitch augmentation has a presynaptic mechanism in humans. The fact that subparalyzing doses of dTC can also block fasciculations suggests that the latter also have a presynaptic origin.

Small doses (0.15–0.25 mg/kg) of succinylcholine are associated with more twitch augmentation than higher doses. This is probably because T1 height is the algebraic sum of neuromuscular blockade and twitch augmentation. The large increases in T1 observed with small doses suggest that twitch augmentation predominates with small doses, and blockade is more prominent if large doses are given. As a result, it seems that twitch augmentation is best studied with a dose of 0.20 mg/kg. This dose could be used in the search of the best method to prevent fasciculations.

The recommendation that 50% more succinylcholine be used if a subparalyzing dose of dTC is administered is based largely on the similarity of the duration of action of 1.5 mg/kg of succinylcholine, preceded by 3 mg/70 kg of dTC, and 1 mg/kg of succinylcholine given alone (1–3). Freund and Rubin (19) administered 0.7 mg/kg of succinylcholine to adult patients. The duration of blockade was the same as if 3 mg of dTC was given followed 3 min later by 1.2 mg/kg of succinylcholine (70% more). In the present study, with a slightly larger dose of dTC (3.5 mg/70 kg), the difference between the ED_{50} was 81%, a similar value.

In conclusion, the results of this study suggest that if a defasciculating dose of dTC is used, the succinylcholine requirement increases nearly twofold. In this case, the adductor pollicis requires 1 mg/kg to be blocked. Considering that some muscles, such as the diaphragm (20), may be more resistant to succinylcholine than the adductor pollicis, a dose as large as 2.0 mg/kg of succinylcholine may be required for tracheal intubation if dTC is used as a defasciculating agent.

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Effects of Intrathecal Injection of the Adenosine Receptor Agonists R-Phenylisopropyl-Adenosine and *N*-Ethylcarboxamide-Adenosine on Nociception and Motor Function in the Rat

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KARLSTEN R, GORDH T Jr, HARTVIG P, POST C. Effects of intrathecal injection of the adenosine receptor agonists R-phenylisopropyl-adenosine and N-ethylcarboxamide-adenosine on nociception and motor function in the rat. Anesth Analg 1990;71:60–4.

R-phenylisopropyl-adenosine, which has an affinity for the adenosine A1 receptor higher than that for the A2 receptor, and N-ethylcarboxamide-adenosine, which has near equal affinity for the A1 and A2 receptors, were injected intrathecally into rats to evaluate differences in antinociceptive effect and motor impairment. Using the tail-immersion test, both compounds had antinociceptive effects. Motor function was evaluated during spontaneous movement in a free space. N-ethylcarboxamide-adenosine rapidly impaired motor function even after low intrathecal doses. R-phenylisopropyl-adenosine also induced motor impairment, but only after high intrathecal doses, and onset was much slower. These results suggest that the receptor selectivity of R-phenylisopropyl-adenosine is diminished at higher doses and that the motor impairment is an A2-receptor-mediated effect. A selective A1 receptor agonist, e.g., R-phenylisopropyl-adenosine, which produces a good antinociceptive effect without motor impairment, is more promising as a drug of possible use for the future treatment of clinical pain.

Key Words: RECEPTORS, ADENOSINE—spinal. ANALGESICS, ADENOSINE RECEPTOR AGONISTS. PAIN, ADENOSINE RECEPTOR AGONISTS.

Several studies (1–5) have demonstrated antinociceptive effects of adenosine agonists following intrathecal (IT) administration to animals. Extracellular adenosine receptors linked to adenylate cyclase have been divided into two classes, A1 and A2 receptors (6). Activation of the A1 receptor decreases adenylate cyclase activity, which in turn decreases the level of intracellular cyclic adenosine monophosphate. The opposite—that is, an increase in adenylate cyclase activity and an increase in intracellular cyclic adenosine monophosphate levels—is seen with activation of the A2 receptor (6). Both A1 and A2 receptors are present in the spinal cord of rats (7,8). This, together with the ability of methylxanthines to inhibit the antinociceptive effects of A1 and A2 receptor agonists (1–4), suggests the involvement of spinal adenosine receptors in mediating the antinociceptive effect of A1 and A2 agonists.

There are several potential adenosine receptor agonists known today, including R-phenylisopropyl-adenosine (R-PIA), which has an affinity for the A1 receptor that is greater than its affinity for the A2 receptor (9–11), and *N*-ethylcarboxamide-adenosine (NECA), which has near equal affinity for the A1 and A2 receptors (10,11). Both have antinociceptive effects when injected intrathecally (1–5). Also, motor impairment has been observed following the IT administration of R-PIA and NECA in mice (2,4) and of cyclohexyl-adenosine (CHA), a selective A1 receptor agonist, in rats (3).

The aim of this study was to investigate the potential differences in antinociceptive effects and motor impairment in rats following IT injection of both an A1 receptor agonist, R-PIA, and one of the most widely used A2 receptor agonists, NECA (11). We also intended to evaluate dose-response differences in regard to these effects and, if possible, identify dose-dependent selectivity of effects.

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Methods

Animals

Male Sprague–Dawley rats (obtained from ALAB, Sollentuna, Sweden), weighing 230–270 g, were used. The animals were anesthetized using intraperitoneal injection of 1.2–1.4 mL of a solution containing chloral hydrate 42.5 g/L, ethanol 90 g/L, propylene glycol 428 mL/L, pentobarbital 9.75 g/L, and magnesium sulfate 21 g/L. A catheter was then inserted through the atlanto-occipital membrane into the spinal subarachnoid space, with the tip of the catheter in the lumbar region (12). The rats were then allowed to recover for a period of 5–6 days. During this time they were kept in separate cages with free access to food and water. They were adapted to the experimental situation in the test cage for 15 min on three consecutive days, before the experiment outlined below took place.

Test of Motor Function

Somatic motor function was scored using a scale from 1 to 4, where 1 represents no motor impairment, 2 represents a partial pareses of the hind legs, 3 represents a full pareses of the hind legs, and 4 represents signs of impairment in the front legs also. The animals were observed during spontaneous movement in a free space.

Nociceptive Tests

Nociceptive testing was performed using the tail-immersion test (13) and the hot-plate test (14). In the tail-immersion test the distal 5 cm of the tail of the animal was immersed in a waterbath maintained at a temperature of 52°C. The time until the animals withdrew the tail was noted. A cutoff time of 25 s was used to avoid tissue damage.

In the hot-plate test the animal was placed on a heated aluminum surface maintained thermostatically at 52°C. The time to a response, defined as licking of the hind paws, or stepping or shaking of the hind legs, was recorded. To avoid tissue damage in this test, a cutoff time of 30 s was used.

The motor and the tail-immersion tests were carried out immediately before (0) and 5, 15, 30, 60, and 90 min after injection of R-PIA; animals receiving NECA were also tested at 120 and 180 min after the intrathecal injection. The hot-plate test was performed before and 15 min after the IT injection. Control animals were given 0.9% saline intrathecally in exactly the same way as those receiving R-PIA or NECA.

Drugs

In the experiment two adenosine receptor agonists were used, R-PIA, an A1 receptor agonist (obtained from Boehringer Mannheim Biochemica, Federal Republic of Germany), and NECA, which has near equal affinity for the A1 and A2 receptors (obtained from Astra Pain Control, Södertälje, Sweden). They were dissolved in saline, except for the highest concentrations of R-PIA (1 and 10 mM), which could be dissolved only after addition of some drops of hydrochloric acid. The solution used for injection was adjusted to pH 7 with buffer. Drugs were injected intrathecally in a volume of 10 μL and the catheter was then flushed with 15 μL of 0.9% saline. Control animals received 25 μL of 0.9% saline instead of drug followed by flush.

In the dose-response experiments, the dosage range for R-PIA was 1–100 nmol (n = 4–5) and for NECA 1–10 nmol (n = 4–5). All drugs, including saline (n = 5), were coded to assure blinding.

In a separate experiment using different rats, theophylline (ACO Läkemedel AB, Solna, Sweden) was then used to antagonize the effects obtained and was injected subcutaneously (SC) in a dose of 50 mg/kg. To evaluate the effects on nociception, one group (n = 4) received theophylline SC 15 min after the IT injection of 100 nmol R-PIA. Theophylline was also administered 90 min after IT injection of 100 nmol R-PIA (n = 4) and 180 min after IT injection of 10 nmol NECA (n = 4) to study the effects on motor impairment.

Statistics

Nociceptive reaction latencies are expressed in seconds and given as mean ± SEM. Statistical differences were evaluated using the Wilcoxon rank-sum test.

Motor effects were scored from 1 to 4, and the values are expressed as means. The Wilcoxon rank-sum test was used for statistical analysis.

P values < 0.05 were considered to represent a statistically significant difference.

Results

Intrathecal Injection of R-PIA

Intrathecal administration of R-PIA in doses from 3.3 to 100 nmol caused a dose-related increase in latency

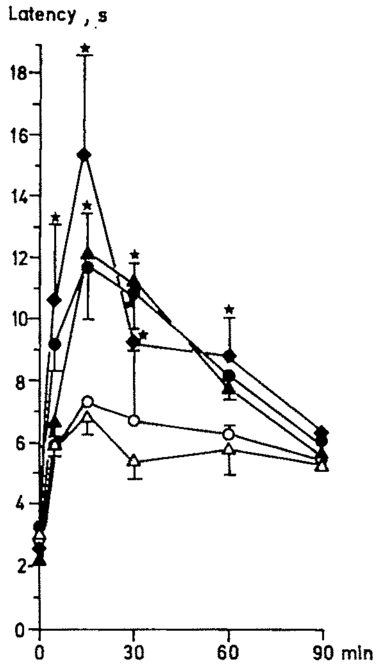

Figure 1. Tail-immersion test. Time-course of latency times following IT injection of R-PIA 1 nmol (○), 3.3 nmol (●), 10 nmol (▲), 100 nmol (◆), and NaCl (△). Values expressed as mean ± SEM for $n = 4–5$. Statistical significance compared with controls is indicated in the figure, $*P < 0.05$.

times compared with control animals in both the tail-immersion and the hot-plate tests. The effect was maximal 15–30 min after drug injection. It lasted about 1 h (Figures 1 and 2).

In rats given 100 nmol of R-PIA, there was an obvious motor impairment with a partial pareses of the hind legs 60 min after the IT injection. This effect progressed to full pareses of the hind legs at 90 min. Theophylline (50 mg/kg SC) completely reversed the motor impairment within 15 min (Figure 3). No motor impairment could be seen in doses up to 10 nmol. Animals that received theophylline (50 mg/kg SC) 15 min after IT injection of 100 nmol R-PIA did not develop motor impairment, and the latency time for the tail-immersion test was reduced back to predrug levels (Figure 4).

Intrathecal Injection of NECA

After IT injection of NECA, the rats also showed a dose-related increase in latency times in the tail-immersion test compared with saline-treated animals. The effect was maximal 15–30 min after drug injection, and lasted less than 1 h (Figure 5). A clear dose-dependent impairment of motor function was seen with all doses 15 min after drug injection, with a duration exceeding that of the nociceptive effect. The motor impairment was completely reversed with injection of theophylline (50 mg/kg SC) 90 min after the IT injection of NECA (Figures 6 and 7).

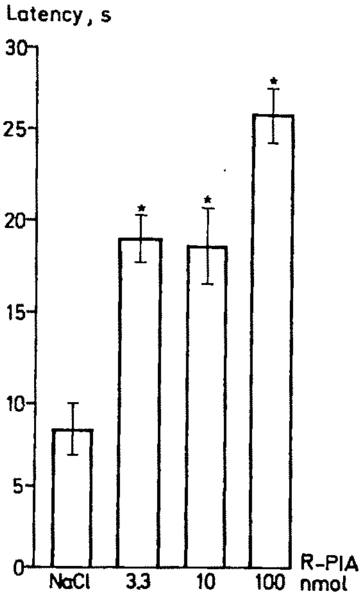

Figure 2. Hot-plate test. Latency times 15 min after IT injection of R-PIA and NaCl. Values expressed as mean ± SEM for $n = 5–8$. Doses in nanomoles as indicated. Statistical significance compared with controls is indicated in the figure, $*P < 0.05$.

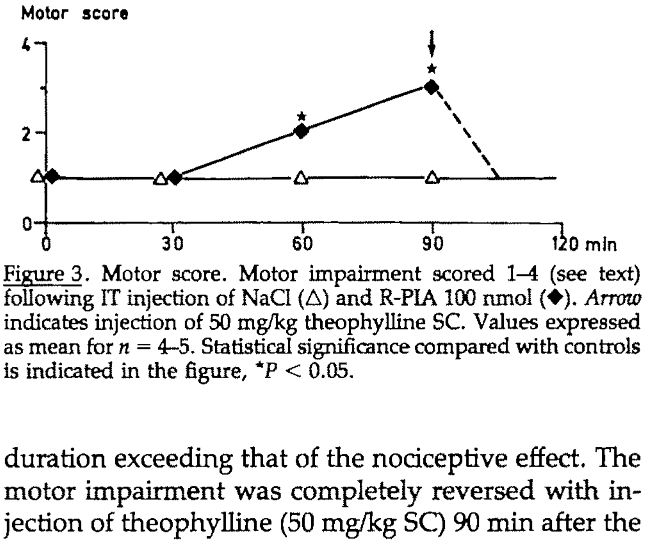

Figure 3. Motor score. Motor impairment scored 1–4 (see text) following IT injection of NaCl (△) and R-PIA 100 nmol (◆). *Arrow* indicates injection of 50 mg/kg theophylline SC. Values expressed as mean for $n = 4–5$. Statistical significance compared with controls is indicated in the figure, $*P < 0.05$.

Because of the severe motor impairment, the hot-plate test could not be used in the studies of NECA.

Discussion

The observation that both R-PIA and NECA induce antinociceptive effects at the spinal level is consistent with earlier studies (1–5). The antinociceptive and motor effects seem to be receptor-mediated because they were completely reversed by theophylline (1–4).

N-ethylcarboxamide-adenosine produced a dose-

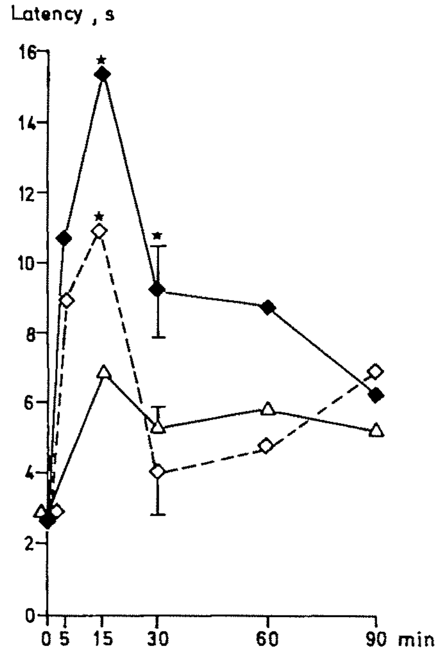

Figure 4. Tail-immersion test. Time-course following IT injection of NaCl (△) and 100 nmol R-PIA in two groups (◆ and ◇). One group (◇) received 50 mg/kg theophylline SC 15 min after IT injection of R-PIA. Values expressed as mean ± SEM for $n = 4$–5. Statistical significance compared with controls is indicated in the figure, $^*P < 0.05$.

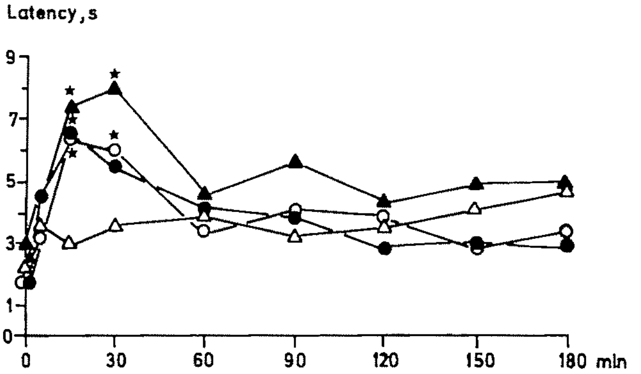

Figure 5. Tail-immersion test. Time-course following IT injection of NECA, 1.0 nmol (○), 3.3 nmol (●), 10 nmol (▲), and NaCl (△). Values expressed as mean for $n = 4$–5. Statistical significance compared with controls is indicated in the figure, $^*P < 0.05$.

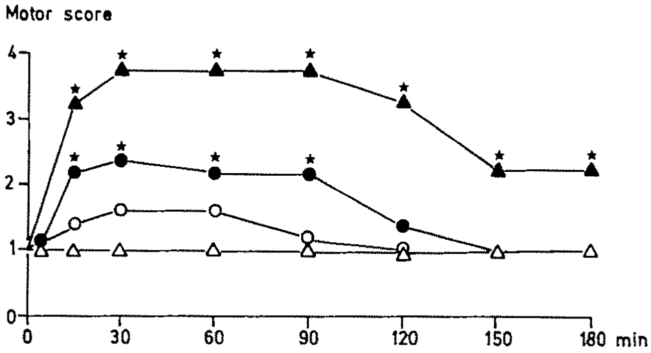

Figure 6. Motor score. Time-course following IT injection of NECA, 1.0 nmol (○), 3.3 nmol (●), 10 nmol (▲), and NaCl (△). Values expressed as mean for $n = 4$–5. Statistical significance compared with controls is indicated in the figure, $^*P < 0.05$.

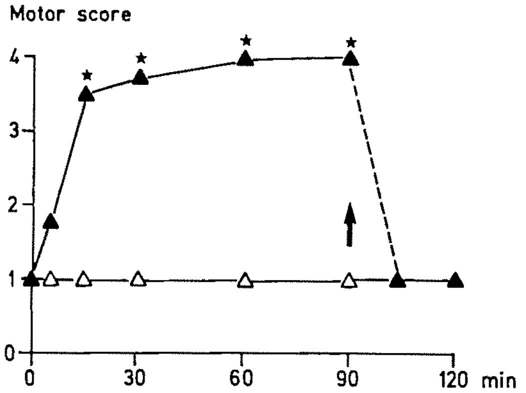

Figure 7. Motor score following IT injection of 10 nmol NECA (▲) and NaCl (△). *Arrow* indicates injection of 50 mg/kg theophylline SC. Values expressed as mean for $n = 4$–5. Statistical significance compared with controls is indicated in the figure, $^*P < 0.05$.

related motor impairment with rapid onset, even after a low IT dose. Even R-PIA induced motor impairment, but only at a dose considerably higher (100 nmol) than that required for antinociception. The onset of the motor effect was slower with R-PIA than with NECA. In an earlier study in mice (4) the duration of the motor impairment induced by NECA, as measured with the rotorod assay, was almost equal to the duration of the antinociceptive effects measured with the tail-flick and hot-plate assays. In our present study, the duration of motor impairment after IT injection of NECA clearly exceeded the duration of antinociception. Another study (3) reported flaccidity in the hind paws at a high dose of CHA, another A1 receptor agonist.

Autoradiographic and binding studies have demonstrated A1 as well as A2 receptors in both the ventral and the dorsal horns of the spinal cord in rats (7,8).

The present observations suggest that the receptor selectivity of R-PIA could be diminished at high doses and that the motor impairment is probably mediated by activation of A2 receptors. Also, R-PIA is more lipophilic and penetrates more slowly into the central nervous system due to partitioning into membranes than the A1/A2 receptor agonist NECA after systemic administration (15). Autoradiographic studies using [^{3}H]NECA and [^{3}H]R-PIA in the lumbar spinal cord of rats after IT injection have demonstrated that R-PIA is confined to the very outermost parts of the spinal cord whereas NECA is distributed throughout the transverse section (5). These differences in physicochemical properties and spinal pharmacokinetics may explain the difference in effect and duration of motor impairment between R-PIA and NECA.

As for other tests of nociceptive reactions, the tail-immersion test may be influenced by motor impairment because the response requires not only a nociceptive signal transmission, but also a motor reflex. In this experiment, the long duration of motor impairment induced by NECA, which clearly exceeded the antinociceptive effect, suggests that the tail-immersion test was not influenced by motor impairment. Even when the animals were completely paralyzed in the hind legs, they were still able to lift the tail from the hot waterbath. Additionally, when testing a high dose of R-PIA (100 nmol), the peak antinociceptive effect was noted well before any motor impairment was observed; and when motor impairment developed, there was no increase in tail-immersion latencies. A possible explanation might be that the drugs inhibit activity in descending motor pathways in the spinal cord, without interfering with the spinal withdrawal reflex.

In summary, there seems to be a distinct difference between the more selective A1 receptor agonist R-PIA (10,11) and the less selective A1/A2 receptor agonist NECA (10,11) with regard to antinociceptive and motor effects. *N*-ethylcarboxamide-adenosine induced motor impairment more rapidly, even at low doses, and had a duration of action on motor function that outlasted its antinociceptive effect. R-phenylisopropyl-adenosine induced significant antinociception without inducing motor impairment in doses up to 10 nmol. These results imply that a more selective A1 receptor agonist, e.g., R-PIA, which produced a good antinociceptive effect without motor impairment in doses up to 10 nmol, is more promising than an A2 receptor agonist as a possible candidate for use in the future in treatment of pain in humans.

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Alfentanil Potentiates Midazolam-Induced Unconsciousness in Subanalgesic Doses

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KISSIN I, VINIK HR, CASTILLO R, BRADLEY EL Jr. Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. Anesth Analg 1990;71:65–9.

The effects of alfentanil on the midazolam dose-response curve for hypnosis was studied with response to the verbal command as an end point in 95 patients. The analgesic effect of alfentanil was studied by measuring the threshold for pain caused by pressure on the trapezius muscle with the use of a dolorimeter in 21 patients. The study was randomized, double-blind, and performed on the unpremedicated patients with ASA physical status I or II. Alfentanil was found to reduce the midazolam ED_{50} value for the induction of anesthesia in a dose-dependent fashion. The smallest dose of alfentanil (3 μg/kg) that caused a marked shift of the midazolam dose-response curve to the left along the dose axis (from the ED_{50} of 270 μg/kg to the ED_{50} of 142 μg/kg, $P < 0.0005$) represents approximately 2% of the alfentanil ED_{50} for induction of unconsciousness (130 μg/kg). Alfentanil (10 μg/kg) caused only a tendency for increase in the pain threshold, whereas a dose of 15 μg/kg significantly increased the pain threshold by 37% ($P < 0.05$). The results demonstrate that alfentanil potentiates the hypnotic effect of midazolam in very small doses. The high potency of alfentanil in this respect, as compared to its analgesic potency, suggests a very specific mechanism of alfentanil-midazolam hypnotic interaction, one that most likely is based on a functional relationship between the GABA receptor-benzodiazepine receptor system and the opioid receptor system in mediation of hypnosis.

Key Words: ANESTHETICS, INTRAVENOUS—midazolam, alfentanil. ANALGESICS, ALFENTANIL. HYPNOTICS, BENZODIAZEPINES—midazolam. INTERACTIONS (DRUGS), BENZODIAZEPINES, OPIOIDS.

Opioid-benzodiazepine combinations usually are used to achieve different components of anesthesia (1–3), a benzodiazepine for hypnosis and an opioid for blockade of responses to noxious stimulation. Additionally, these two groups of agents interact favorably with regard to the hypnotic component of anesthesia. In a previous study we found that the hypnotic interaction between midazolam and alfentanil is synergistic: approximately one-fourth of the single-drug ED_{50} dose for each of the two agents is needed in combination to induce anesthesia in 50% of patients (4).

It is a common practice at present to combine the induction dose of midazolam with a relatively small dose of an opioid to provide analgesia. There are indications that opioids, even in small doses, can enhance the hypnotic effect of benzodiazepines (5). We suggest that the potency of opioids for enhancing the hypnotic effect of benzodiazepines may be greater than their analgesic potency. The aim of the present study was to determine the minimal dose of alfentanil necessary to reduce by half the midazolam ED_{50} value for induction of anesthesia.

Methods

This randomized double-blind study, which was approved by the Institutional Human Investigation Committee, included 116 ASA physical status I or II adult women. The patients were 18–60 yr of age, with a weight range of 45–90 kg. Patients who had received benzodiazepines or opioids within 1 mo of the investigation were excluded from the study. None of the patients received any premedication.

Two series of investigations were performed. In the first series, we studied the effect of alfentanil on

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Table 1. Doses of Alfentanil and Midazolam Administered in the First Series

Group	Subgroup	Doses (μg/kg) Alfentanil	Doses (μg/kg) Midazolam
NO ALF	1	Saline	80
	2	Saline	110
	3	Saline	160
	4	Saline	240
	5	Saline	350
ALF 3	1	3	80
	2	3	110
	3	3	160
	4	3	240
ALF 6	1	6	80
	2	6	100
	3	6	120
	4	6	150
	5	6	180
ALF 20	1	20	50
	2	20	60
	3	20	70
	4	20	90
	5	20	110

midazolam-induced unconsciousness; in the second series, we studied the analgesic effect of alfentanil. In the first series, the inability to open eyes on command was used as an end point of anesthesia. Absence of the response to two consecutive voice commands determined by the observer blinded to the treatment was regarded as a positive response to the agent(s). The patients were assigned to one of the four groups in which midazolam dose-response curves were determined with the addition of different doses (fixed for each group) of alfentanil or normal saline (control group). The following doses of alfentanil were used (μg/kg): 3 (ALF 3), 6 (ALF 6), and 20 (ALF 20). These were selected on the basis of the alfentanil dose-response curve obtained in our previous study (4) and represent approximately 2%, 5%, and 15% of the alfentanil ED_{50} for induction of unconsciousness. Each group consisted of 25 (or 20) patients divided into five (or four) subgroups of five patients each, and there were predetermined doses of midazolam in each subgroup. The choice of midazolam doses was based on our previous study and on several pilot observations.

The administered doses are given in Table 1. Dose selection was made randomly with blocked allocation of patients. A block size of 19 patients was used: four treatments (NO ALF, ALF 3, ALF 6, ALF 20) with 4–5 doses of midazolam for each treatment. A random order in the first block was repeated in four subsequent blocks. Doses of midazolam and alfentanil were expressed in terms of the salt.

The drugs were injected over 10 s in an upper extremity into a rapidly flowing intravenous infusion via the port nearest the intravenous catheter. Midazolam was injected first, followed 1 min later by alfentanil (or saline in the NO ALF group). The end point (unconsciousness) was determined 3 min after the first injection. After determining the response to verbal command, all patients received additional anesthesia if needed to assure that anesthesia was adequate before starting the surgical procedure. Times between injections of drugs and determination of the end point were based on the times to peak effect for these agents: 3 min for midazolam (5,6) and 2 min for alfentanil (7). With combined drug administration, both drugs were injected so that synchronization of the peak effects would occur. These time intervals were selected on the basis of a preliminary study.

In the second series, the analgesic effect of alfentanil was determined by measuring the pain threshold to pressure on the trapezius muscle. A dolorimeter (PTH model, Pain Diagnostics and Thermography Co., Great Neck, N.Y.) was used to measure the pain threshold. The pressure was increased at a constant rate until the patients reported the feeling of pain. In each patient the measurement was made twice, before and 5 min after intravenous injection of alfentanil or saline. Three groups of seven patients were used in this series: 15 μg/kg alfentanil, 10 μg/kg alfentanil, and normal saline. The drug was injected intravenously over 10 s. The patients were assigned randomly to one of these groups. The pressure threshold was measured by an investigator who was unaware of what drug or dose was used.

In the first series, dose-response curves and ED_{50} values were determined with the use of a probit analysis (8). Differences among the ED_{50} values were compared by using pairwise *t*-test on the log ED_{50} values. In the second series, the mean percent change in pain threshold was compared among the groups by a one-way analysis of variance (9). All data were collected over a 5-mo period.

Results

The study groups were comparable with respect to age and weight (Table 2). The midazolam dose-response curves for induction of anesthesia are presented in Figure 1. The midazolam ED_{50} values progressively decreased with increasing dose of alfentanil (Table 3). When midazolam was used alone, its ED_{50} value was 270 μg/kg (95% confidence limits, 187–421 μg/kg). The addition of 3 μg/kg alfen-

Table 2. Characteristics of Patients

Variable	Groups			
	NO ALF	ALF 3	ALF 6	ALF 20
Age (yr)	35 ± 7	35.1 ± 8	30.9 ± 5	29.0 ± 7
Weight (kg)	71 ± 11	70 ± 12	65.1 ± 10	68 ± 9
Number of patients	25	20	25	25

Data are reported as mean ± SD; all patients were women.

tanil shifted the midazolam ED_{50} value to 142 μg/kg (110–215 μg/kg) with a high level of statistical significance ($P < 0.0005$). Doubling the dose of alfentanil (to 6 μg/kg) resulted in a tendency for an additional shift in the midazolam ED_{50} value. When alfentanil was used in a dose of 20 μg/kg, the midazolam ED_{50} value reduced further, to 68 μg/kg (54–83 μg/kg).

The effect of alfentanil on pain threshold is presented in Figure 2. Although 10 μg/kg alfentanil increased the pain threshold by 22%, this increase was not significantly different from the pain threshold changes in the saline group (a decrease of 12%). Only 15 μg/kg alfentanil caused a statistically significant increase in the pain threshold (37% ± 9%, with $P < 0.05$ from the saline group).

Discussion

The midazolam dose-response curve without the addition of alfentanil was close to that reported in our previous study (270 μg/kg, 95% confidence limits 187–421 μg/kg vs 220 μg/kg, 95% confidence limits 150–500 μg/kg in the previous study) (4). Alfentanil in a very small dose of 3 μg/kg reduced by half the midazolam ED_{50} value for unconsciousness. The comparison of this dose of alfentanil with the alfentanil dose-response curve for unconsciousness obtained in the previous study indicates that it represents approximately 2% of the alfentanil ED_{50} value for unconsciousness. We did not use doses of alfentanil lower than 3 μg/kg. However, the high level of statistical significance in the difference between midazolam ED_{50} values with and without alfentanil (270 vs 142, $P < 0.0005$) suggests that alfentanil doses even lower than 3 μg/kg would probably also be effective in potentiation of the hypnotic effect of midazolam. These results correlate well with the observation by Halliday et al. that 150 μg alfentanil (per patient) increased the percentage of patients who had anesthesia induced with 300 μg/kg midazolam from 60% to 85% (5).

In Table 3, the effect of alfentanil on the midazolam-induced unconsciousness is presented in terms of midazolam hypnotic potency. The table demonstrates that with doses of alfentanil of 3 and 6 μg/kg, the potency of midazolam increased to 1.90 and 2.16, respectively. Direct contribution of alfentanil in terms of its own hypnotic effect with these two doses is insignificant because they represent only 2% and 5% of the alfentanil hypnotic ED_{50} value of 130 μg/kg (4). With 20 μg/kg alfentanil, its direct contribution is more marked (15%), however, midazolam hypnotic potency is also much higher (3.97).

We observed a statistically significant analgesic effect of alfentanil with the 15-μg/kg dose (with seven patients in each group). It is likely that the tendency for analgesia with the 10-μg/kg dose would become a statistically significant effect if the number of patients were increased. Hill et al. studied the analgesic effect of alfentanil in humans using a method of electrical stimulation of the tooth. They have found that the analgesic effect of alfentanil can be reproduced in the dose range similar to that in our study, 5–15 μg/kg (10).

The comparison of alfentanil doses enhancing the midazolam hypnotic effect with its analgesic doses shows that this opioid provides a profound reduction of the midazolam ED_{50} value for the hypnotic effect (from 270 to 142 μg/kg, $P < 0.0005$) in the dose (3 μg/kg) that is below the dose with borderline analgesic effect (10 μg/kg). The investigators who discovered alfentanil are convinced that "the more potent the compounds, the more specific they are" (11). If we logically follow this assumption, our study demonstrates that alfentanil is more specific as an enhancer of the hypnotic effect of benzodiazepines than analgesic because we can do this with a smaller dose of alfentanil.

It is a common anesthetic practice today to give small supplementary doses of short-acting opioids in conjunction with benzodiazepines or other hypnotic agents. Drugs such as alfentanil or fentanyl are presumably given primarily for antinociceptive effect, to enhance the analgesic component of anesthesia. Results of this study indicate that enhancement of the hypnotic component of benzodiazepine-induced anesthesia might be the most important underlying mechanism for the beneficial result with such a combination.

Benzodiazepines and opioids act at two separate receptor sites. We suggest that there is a functional link between the GABA receptor-benzodiazepine receptor system and the opioid receptor system in the mediation of hypnosis. Stella et al. (12) have reported that in surgical patients naloxone decreased the percentage of patients rendered unconscious by diazepam. Because naloxone was used in a small dose (6

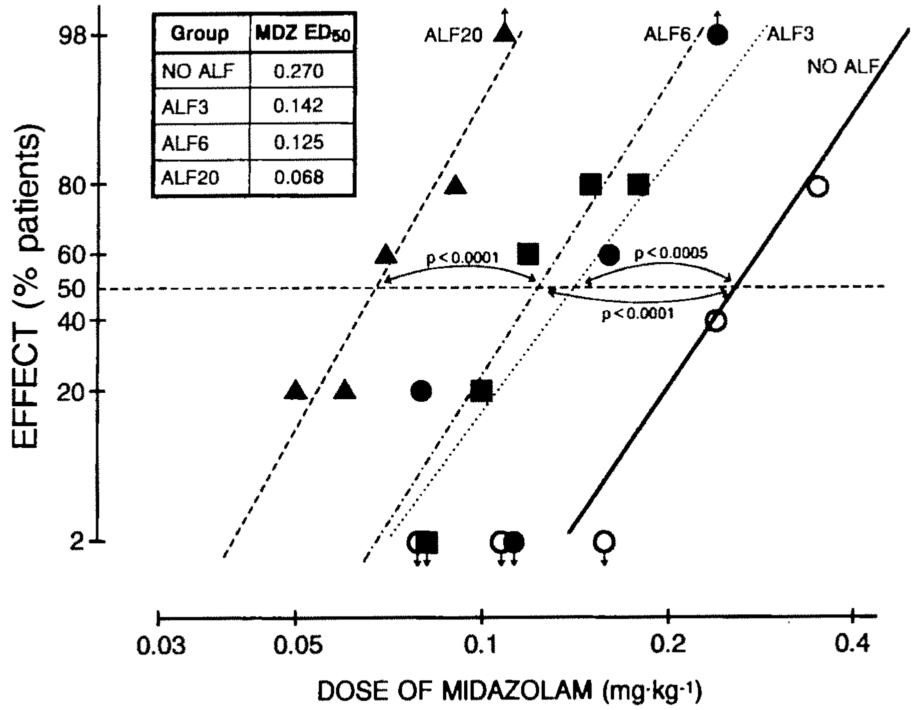

Figure 1. Effect of alfentanil on the midazolam dose-response curves for induction of anesthesia. NO ALF (*open circles*)—the midazolam dose-response curve without the addition of alfentanil (saline only). ALF 3 (*filled circles*), ALF 6 (*squares*), and ALF 20 (*triangles*)—the midazolam dose-response curves with the addition of alfentanil in the doses 3, 6, and 20 μg/kg, respectively. Each circle (square or triangle) represents the effect in a subgroup of five patients at the indicated dosage. *Arrow* superimposed on symbols indicates that their actual locations are higher or lower (restriction due to probit scale of the figure). The *inset* represents midazolam ED_{50} values for the four dose-response curves.

Table 3. Potentiation of the Hypnotic Effect of Midazolam by Alfentanil

Group number	Dose of alfentanil (μg/kg)	Hypnotic ED_{50} for midazolam (μg/kg)	Midazolam hypnotic potency
1	0	270 (187–421)	1.00
2	3	142 (110–215)^a	1.90
3	6	125 (99–155)^{a,b}	2.16
4	20	68 (54–83)^c	3.97

Ninety-five percent confidence limits are given in parentheses.
$^a P < 0.0005$ in comparison with group 1.
$^b P > 0.05$ in comparison with group 2.
$^c P < 0.0001$ in comparison with groups 1, 2, and 3.

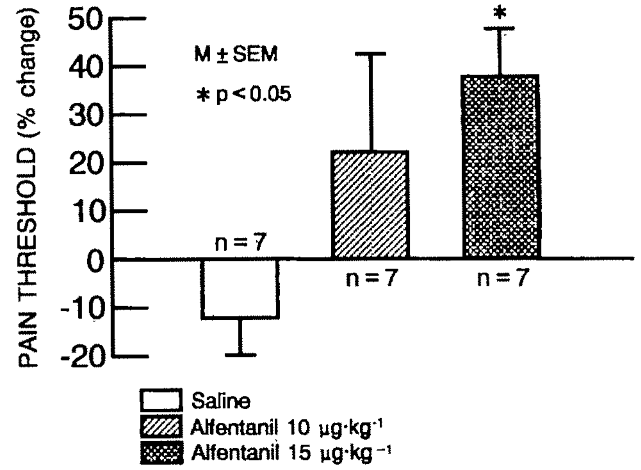

Figure 2. Effect of alfentanil on the pain threshold. The columns represent three groups of patients. *Statistically significant difference from control (saline) group.

μg/kg), the nonspecific, analeptic effect of this agent probably can be ruled out. This finding may suggest that an endogenous opioid system provides some complementary action for benzodiazepine-induced hypnosis. Most likely, alfentanil-induced potentiation of the hypnotic effect of midazolam represents a functional interaction, when two different systems are complementary for the common effect.

In conclusion, alfentanil in subanalgesic doses potentiates the hypnotic effect of midazolam.

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Absence of Abundant Saturable Binding Sites for Halothane or Isoflurane in Rabbit Brain: Inhaled Anesthetics Obey Henry's Law

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LOCKHART SH, EGER EI II. Absence of abundant saturable binding sites for halothane or isoflurane in rabbit brain: inhaled anesthetics obey Henry's law. Anesth Analg 1990;71:70–2.

We tested whether the existence of saturable binding sites for anesthetics causes the solubility of halothane or isoflurane in rabbit brain not to obey Henry's law. For each anesthetic, we measured brain/gas partition coefficients (paired samples) at approximately 0.05 MAC and 5 MAC at 38.5°C. In addition, for halothane, brain/gas partition coefficients (paired samples) were determined at 0.05 MAC and 2 MAC. The values for halothane at 0.05 MAC, 2 MAC, and 5 MAC did not differ; values for isoflurane at 0.05 MAC and 5 MAC did not differ. Over the range of anesthetic partial pressures studied, no evidence for saturable binding was found. We conclude that the solubility of halothane and isoflurane in brain is independent of the partial pressure applied; inhaled anesthetics obey Henry's law.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. SOLUBILITY—halothane, isoflurane. PHYSICS—Henry's law.

Evers et al. (1) have suggested that inhaled anesthetics act by binding to abundant saturable molecular sites in brain. Using ^{19}F magnetic resonance spectroscopy to study spontaneously breathing rats, they found that cerebral halothane concentrations do not increase in proportion to inspired concentrations when the latter exceed 3%. From these data they derived the presence of anesthetic binding sites that become saturated at anesthetic partial pressures greater than 3.0 minimum alveolar concentration (MAC). If they are correct, the solubility of anesthetics in brain should decrease at high anesthetic partial pressures: that is, inhaled anesthetics should not obey Henry's law. Previously, Coburn and Eger (2) showed that inhaled anesthetics obey Henry's law for concentrations between 0.01 and 1.0 MAC but did not report on the higher multiples of MAC studied by Evers et al. Thus, we studied whether the solubility of halothane or isoflurane decreases at partial pressures exceeding 1.0 MAC in rabbit brain.

Methods

With approval of the University of California Committee on Animal Research, 18 male New Zealand White rabbits, weighing 3.5–4.5 kg, were killed by inhalation of carbon dioxide. The brain was excised and the dura removed. For each brain, 13 mL of saline was placed in a graduated cylinder, combined with 7 mL of brain (measured by displacement), and homogenized with a Kinematic CH-6010 homogenizer. The homogenate was equally divided between two 30-mL glass syringes, prepared by lubricating the barrels with a small amount of silicone grease. For each anesthetic (halothane and isoflurane), six brains were homogenized and one syringe was equilibrated with a partial pressure of approximately 0.05 MAC, the other with a partial pressure of approximately 5 MAC. In an additional set of experiments, six brains were homogenized and one sample of homogenate was equilibrated with approximately 0.05 MAC halothane, the other with approximately 2 MAC halothane.

Each syringe received about 13 mL of air containing halothane or isoflurane from premixed tanks with anesthetic partial pressures approximately equal to the above MAC values. To achieve partial pressures of 5 MAC, anesthetic was added to the syringe, the syringes shaken, and the gaseous portion discharged. This procedure was repeated five times for

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Table 1. Partition Coefficients for Halothane and Isoflurane in Rabbit Brain

	Halothane			Isoflurane	
	Low	Mid	High	Low	High
Percent anesthetic	0.036 ± 0.006	2.03 ± 0.23		0.063 ± 0.008	6.39 ± 0.82
Brain/gas partition coefficient	4.79 ± 0.54	5.12 ± 0.55		2.32 ± 0.24	2.46 ± 0.20
Percent anesthetic	0.029 ± 0.005		4.84 ± 0.25		
Brain/gas partition coefficient	4.57 ± 0.37		4.78 ± 0.55		

All values are mean ± SD. For each set of paired determinations, $n = 6$.
Low, low concentration; mid, middle halothane concentration; and high, high concentration.

halothane and four times for isoflurane. Finally, the homogenate-gas mixture was placed in a tonometer in a waterbath at 38.5°C and allowed to equilibrate for 2 h. Every 15 min the syringes were removed from the waterbath and shaken vigorously.

After the 2-h period of equilibration, the concentration of the gas phase was measured by gas chromatography. The chromatograph contained an 1/8-in. column packed with 10% SF-96 Chromosorb WHP 60/80 mesh and a flame ionization detector with an air-hydrogen gas mixture. The column and detector temperatures were 40°C and 150°C, respectively.

An aliquot (5 mL) of the homogenate was injected into an evacuated flask of precisely known volume. Each flask was approximately 600 mL. The flask was placed in the waterbath at 38.5°C and warmed before equilibration with ambient pressure. The flask remained in the waterbath for 1 h and was vigorously shaken at 15-min intervals. At the end of the period, 20 mL of air was added to the flask and barbotaged 15–20 times. The mixture was analyzed by gas chromatography.

The homogenate/gas partition coefficient (HG) was calculated as follows:

$$HG = [(V_f + 20\text{ mL} - V_h)/V_h]\,[C_f/(C_s - C_f)], \qquad (1)$$

where V_f is the volume of the flask, C_f is the concentration of anesthetic gas in the flask, V_h is the volume of homogenate, and C_s is the concentration of anesthetic gas in the syringe. The brain/gas partition coefficient (BG) was calculated as follows:

$$BG = [(V_h)(HG) - (V_s)(SG)]/V_b, \qquad (2)$$

where V_s is the volume of the saline in the aliquot of homogenate, SG is the saline/gas partition coefficient, and V_b is the volume of brain in the aliquot of homogenate.

Although the saline/gas partition coefficients for halothane and isoflurane previously have been reported to be independent of anesthetic partial pressure (for values up to 1 MAC), the values used in our calculations were independently determined. The value for SG is determined in a manner identical to that for HG, except that V_s is substituted for V_h in Equation (1).

We compared the values for brain/gas partition coefficients at high and low concentrations using paired and unpaired *t*-tests. The null hypothesis: BG low > BG high was tested using a one-sided test; the null hypothesis: BG low = BG high was tested using a two-sided test. For saline/gas partition coefficients, the null hypothesis: SG low = SG high was tested using unpaired *t*-tests. A *P* value of <0.05 was considered statistically significant. All values are reported as mean ± SD.

Results

The solubility of halothane or isoflurane in rabbit brain was similar at low and high partial pressures (Table 1). For halothane, values were not significantly different at partial pressures of 0.05 MAC, 2 MAC, and 5 MAC; for isoflurane, values were not significantly different at 0.05 MAC and 5 MAC. At 0.05 MAC and 5 MAC, respectively, saline/gas partition coefficients for halothane were 0.54 ± 0.05 ($n = 6$) and 0.55 ± 0.07 ($n = 6$), coefficients for isoflurane were 0.52 ± 0.05 ($n = 6$) and 0.53 ± 0.06 ($n = 6$). Values are reported as mean ± SD.

Discussion

We have found the brain/gas partition coefficients for halothane and isoflurane to be independent of the anesthetic partial pressure applied for partial pressures ranging from 0.05 MAC to 5 MAC. Anesthetic solubility does not, therefore, decrease at high anesthetic partial pressures. That is, inhaled anesthetics obey Henry's law. Consequently, contrary to Evers et al., we find no evidence for saturation of anesthetic binding sites at anesthetic partial pressures greater than 3 MAC. If such saturable binding sites exist, they are not detectable using our methods and must be few in number.

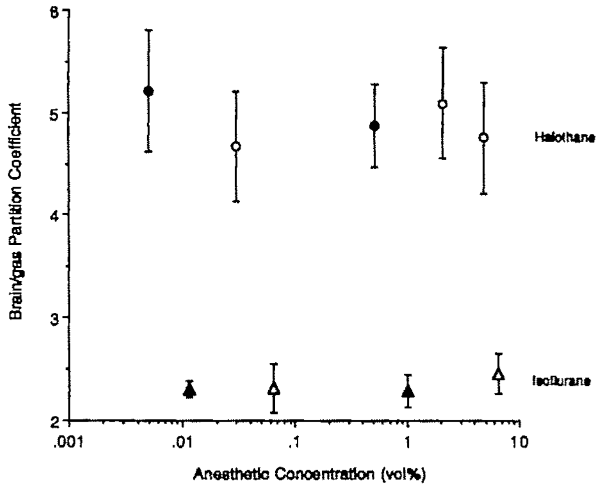

Figure 1. Brain/gas partition coefficients (mean ± SD) are independent of anesthetic concentration for halothane and isoflurane; inhaled anesthetics obey Henry's law. Our values for halothane (○) at 0.05 MAC, 2 MAC, and 5 MAC are comparable to those of Coburn and Eger (2) (●) at 0.01 MAC and 1 MAC. Similarly, values for isoflurane (△) at 0.05 MAC and 5 MAC are comparable to those of Coburn and Eger (▲) at 0.01 MAC and 1 MAC.

Our findings extend and confirm those of Coburn and Eger (2), who report anesthetic solubility in rabbit and human brain to be independent of anesthetic partial pressure, at pressures of up to 1 MAC. Additionally, our coefficient values are comparable to those previously reported at 0.01 MAC and 1 MAC (2) (Figure 1).

Our results are consistent with a recent correction reported by Evers et al. in a letter to *Nature* (3). In rats allowed to breathe spontaneously for 1 h and then decapitated, they reported that the brain/blood halothane concentration ratio was constant for inspired concentrations ranging from 0.75% to 3.25%. They also found in separate determinations that blood/gas partition coefficients for halothane were the same at concentrations of 1% and 3%. From these data, it seems plausible that the brain/gas partition coefficient for halothane at 1% and 3% would be the same. However, in their correction, brain/gas partition coefficients were not determined nor were contemporaneous measurements of brain/blood and blood/gas partition coefficients made in the same animal. Moreover, only halothane was studied and over a more limited range of concentrations than in the present study.

Our results do not explain the findings of Evers et al. that inspired and cerebral halothane concentrations are not proportional when inspired concentrations exceed 3%. Possibly, in spontaneously breathing animals, anesthetic-induced depression of ventilation accounts for the failure of cerebral halothane concentrations to increase in proportion to inspired concentrations. This mechanism might apply because cerebral anesthetic partial pressure closely approximates arterial anesthetic partial pressure (and not inspired partial pressure) (4), and the latter does not increase in proportion to inspired partial pressures in the presence of ventilatory depression.

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Contrast Media Adversely Affect Oxyhemoglobin Dissociation

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KIM S-J, SALEM MR, JOSEPH NJ, MADAYAG MA, CAVALLINO RP, CRYSTAL GJ. Contrast media adversely affect oxyhemoglobin dissociation. Anesth Analg 1990;71:73–6.

Effects of ionic (Hypaque-76) and nonionic (Isovue-370 and Omnipaque-350) contrast media on oxyhemoglobin dissociation of normal human red blood cells were evaluated. In series 1, 4-mL venous blood samples were obtained from 15 normal human volunteers. One blood sample served as control, and 1 mL of either of the three contrast media was added in vitro to the other 4-mL blood samples. P_{50} values were estimated from the linear portion of the oxyhemoglobin dissociation curve obtained by tonometry. Determinations of P_{50} were performed at either pH 7.4 or 7.2. At pH 7.4, P_{50} in the absence of contrast media was 26.3 ± 0.4 mm Hg (mean ± SEM). The contrast media caused comparable decreases in P_{50} from this value (Hypaque-76, 20.0 ± 0.5 mm Hg; Omnipaque-350, 21.6 ± 0.4 mm Hg; Isovue-370, 20.7 ± 0.4 mm Hg). Reducing pH to 7.2 in the absence of contrast media increased P_{50} to 33.3 ± 1.0 mm Hg, evidence of the Bohr effect. The presence of contrast media either completely abolished (Hypaque-76 and Omnipaque-350) or markedly attenuated (Isovue-370) this effect. In series 2 (five patients), blood samples were withdrawn from the external iliac artery during injection of Isovue-370 (60–78 mL) into the proximal abdominal aorta to evaluate peripheral vascular disease. Measurement of P_{50} of these samples yielded findings consistent with those of series 1. The present findings demonstrate that both ionic and nonionic contrast media increase the affinity of hemoglobin for oxygen and, therefore, that they may inhibit oxygen delivery to body tissues.

Key Words: OXYGEN, OXYHEMOGLOBIN DISSOCIATION—contrast media. BLOOD, HEMOGLOBIN—oxygen dissociation.

Previous studies conducted in vitro demonstrated that ionic contrast media cause a leftward shift of the oxyhemoglobin dissociation curve, implying impaired release of oxygen from hemoglobin in red blood cells (RBCs) (1,2). This effect was attributed to the greater osmolality of these contrast agents compared with plasma, causing movement of water and chloride ions out of the red cell and of hydroxyl ions into the red cell, and thus an increase in intracellular pH (2). Recently, nonionic contrast agents have become available that have reduced osmolality and that, in addition, may have fewer toxic side effects than ionic agents (3,4). The improved physical and chemical characteristics of the nonionic contrast agents may render them free of the adverse effects on oxyhemoglobin dissociation observed with ionic contrast agents. The present study was conducted to test this hypothesis by comparing in vitro the effects of nonionic and ionic contrast agents on oxyhemoglobin dissociation characteristics of human RBCs. In addition, blood samples were obtained during diagnostic angiography to determine the effects on oxyhemoglobin dissociation of clinically achieved concentrations of a nonionic contrast medium.

Methods

Informed consent for collection of blood samples was obtained from human volunteers and patients undergoing angiography.

Series 1. In Vitro Studies

Blood samples were collected from the median cubital vein of 15 healthy human volunteers of either sex into heparinized vacuum tubes (Becton Dickinson Vacu-

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Table 1. Lack of Effect of 1:4 Hemodilution With Isotonic Saline on P_{50} With pH at 7.4 and 7.2

	pH = 7.4 (n = 10)		pH = 7.2 (n = 5)	
	Blood alone	Blood + saline	Blood alone	Blood + saline
pH	7.42 ± 0.01	7.41 ± 0.01	7.20 ± 0.01	7.20 ± 0.01
Hct (%)	43.7 ± 0.9	34.2 ± 0.7*	45.1 ± 1.1	36.2 ± 1.2*
P_{50} (mm Hg)	26.3 ± 0.4	26.3 ± 0.4	33.6 ± 1.3	33.1 ± 1.0

Hct, hematocrit.
Values are mean ± SEM.
*$P < 0.01$ vs blood alone at respective pH.

tainer Systems). Four-milliliter aliquots of this blood were thoroughly mixed with 1 mL of an ionic contrast medium, Hypaque-76 (Winthrop Pharmaceuticals), or 1 mL of either of two nonionic contrast media, Omnipaque-350 (Winthrop Pharmaceuticals) or Isovue-370 (E. R. Squibb and Sons), resulting in comparable decreases in hematocrit values because of hemodilution. The baseline hematocrit value (45.1% ± 1.1%) was reduced to 32.8% ± 2.0%, 32.5% ± 1.4%, and 34.2% ± 1.1% for Hypaque-76, Omnipaque-350, and Isovue-370, respectively. A fourth 4-mL aliquot of blood, free of contrast media, served as control. The validity of using an undiluted sample of blood for the control measurements was confirmed in preliminary studies demonstrating lack of effect of dilution with 1 mL of isotonic saline on P_{50} values at pH 7.4 and 7.2 (Table 1).

The blood samples were equilibrated in a tonometer (Instrumentation Laboratory, model 237) with three different low-oxygen gas mixtures at 38°C (3.0%, 3.5%, or 4.0% O_2; 5.6% CO_2; balance N_2). These gases were selected to yield samples with Po_2 values in the linear portion of the oxyhemoglobin dissociation curve with Pco_2 values equal to 40 mm Hg. Each blood sample was equilibrated within the tonometer for 15 min. At that time, an aliquot of blood was drawn to measure Po_2, Pco_2, and pH electrometrically (Instrumentation Laboratory, model 1306), and percent oxyhemoglobin in a CO-Oximeter (Instrumentation Laboratory, model 482). Hematocrit was measured with a microcapillary centrifuge. The partial pressure of oxygen at which hemoglobin was 50% saturated with oxygen, i.e., the P_{50}, was estimated from linear regression analysis of the individual data points (5). To assess the Bohr effect, P_{50} was estimated at normal pH 7.4 and again at pH 7.2. The contrast media themselves caused significant decreases in pH of the blood samples (to 7.021–7.219), which usually necessitated addition of sodium bicarbonate to achieve the desired pH values.

Series 2. In Vivo Studies

Blood samples from five patients of either sex (average weight, 64 kg) were obtained before, during, and after injection of Isovue-370 to evaluate peripheral vascular disease. The blood sample before injection was withdrawn through a 5F pigtail (Cook) catheter advanced through a 6F sheath into the proximal abdominal aorta via a femoral artery puncture. The contrast medium was then injected into this catheter, while a blood sample was withdrawn from the external iliac artery via the sheath. A final blood sample was withdrawn from this site 2 min after injection of the medium. The Isovue-370 was injected at a rate of 6 mL/s for 10–13 s (total volumes injected, 60–78 mL). The volume of blood withdrawn for oxyhemoglobin analysis was 7 mL. Analysis of blood samples for change in P_{50} after in vivo administration of contrast medium was performed as described above for the in vitro studies; however, only pH equal to 7.4 was studied.

Effects of contrast media and pH variations on P_{50} were tested for statistical significance using Student's t-test for paired samples. Differences were considered statistically significant if $P < 0.05$. Data are presented as mean ± SEM.

Results

In Vitro Findings

Table 2 summarizes the effects of Hypaque-76, Omnipaque-350, and Isovue-370 on P_{50} at pH values of 7.4 and 7.2. At pH 7.4, P_{50} in the absence of contrast media was 26.3 ± 0.4 mm Hg. All three contrast media caused similar decreases in P_{50} below this value (Hypaque-76, 20.0 ± 0.5 mm Hg; Omnipaque-350, 21.6 ± 0.4 mm Hg; Isovue-370, 20.7 ± 0.4 mm Hg). Furthermore, addition of contrast media either completely abolished (Hypaque-76 and Omnipaque-350) or markedly attenuated (Isovue-370) the increase in P_{50} accompanying decreased pH.

Table 2. In Vitro Effects of Contrast Media on P_{50} With pH at 7.4 and 7.2

	P_{50} (mm Hg)	
	pH = 7.4	pH = 7.2
Control	26.3 ± 0.4	33.6 ± 1.3^a
Hypaque-76	20.0 ± 0.5^b	21.6 ± 0.6^b
Omnipaque-350	21.6 ± 0.4^b	23.7 ± 0.7^b
Isovue-370	20.7 ± 0.4^b	23.6 ± 0.5^{a,b}

Values are mean ± SEM; $n = 5$.
$^a P < 0.01$, from pH 7.4.
$^b P < 0.05$, from control at respective pH.

Table 3. In Vivo Effects of Isovue-370 on Hematocrit and P_{50} at pH 7.4

	pH	Hct (%)	P_{50} (mm Hg)
Before injection	7.40 ± 0.01 (7.44 ± 0.02)^a	38.5 ± 1.4	25.3 ± 0.4
During injection	7.43 ± 0.01 (7.13 ± 0.01)	21.0 ± 3.5^b	17.6 ± 1.6^b
After injection	7.40 ± 0.01 (7.41 ± 0.02)	34.4 ± 1.0	25.4 ± 0.3

Values are mean ± SEM; $n = 5$.
^{a}pH values before in vitro correction.
$^b P < 0.01$, from before injection.

In Vivo Findings

Table 3 summarizes effects of in vivo injection of Isovue-370 on P_{50}, pH, and hematocrit. Blood samples obtained 5 s after injection of Isovue-370 revealed reduction in hematocrit, from 38.5% ± 1.4% to 21.0% ± 3.5%, and pH, from 7.44 ± 0.02 to 7.13 ± 0.01. The value for P_{50} after normalization of pH to 7.4 decreased from 25.3 ± 0.4 mm Hg to 17.6 ± 1.6 mm Hg. By 2 min after injection of Isovue-370, all variables had returned to preinjection values. Figure 1 demonstrates the leftward shift of the oxyhemoglobin dissociation curve implied by the P_{50} values obtained after the in vivo injection of Isovue-370.

Discussion

The main findings of the present study were as follows. (a) The ionic and nonionic contrast media caused significant 25% decreases in P_{50} at normal pH and either prevented or significantly attenuated the Bohr effect on P_{50} in response to reduced pH. (b) The concentration of contrast medium in the aorta during injection for evaluation of peripheral vascular disease was sufficient to cause a significant decrease in P_{50} after normalization of pH.

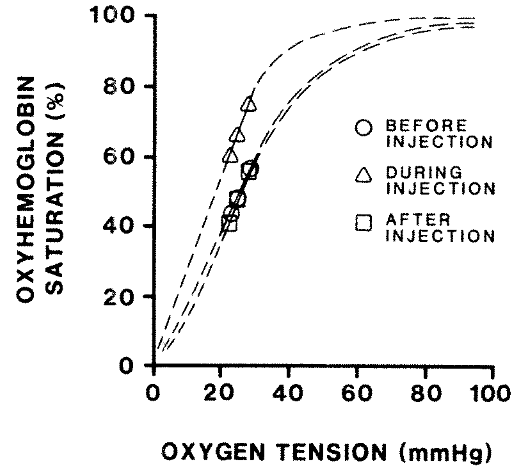

Figure 1. Oxyhemoglobin dissociation curve with pH normalized to 7.4 before injection, during injection, and 2 min after injection of Isovue-370 into proximal abdominal aorta to evaluate peripheral vascular disease in five patients. Segments of curves outside of the range of in vitro measurements were extrapolated and are indicated on the figure by a *broken line*.

Previous in vitro studies with ionic contrast media suggested that the change in P_{50} caused by these media may be due to their tendency to disrupt the normal relationship between extracellular and intracellular pH (1,2,6). It was theorized that shrinkage of the RBCs due to increased plasma osmolality alters transmembrane potential, resulting in loss of intracellular hydrogen ions. The increase in intracellular pH then, it was believed, leads to a leftward shift of the oxygen hemoglobin dissociation curve. The present findings showing that the ionic and nonionic contrast media caused similar effects on oxyhemoglobin dissociation of RBCs do not support the proposal that increased plasma osmolality produced by contrast media is one cause of changes in RBC P_{50}.

Although RBC 2,3-diphosphoglycerate and adenosine triphosphate levels were not measured in the present study, previous reports demonstrated that they are not changed by contrast agents (6), and thus these factors probably also did not contribute to the observed changes in P_{50}. Therefore, the mechanism by which the contrast media cause dissociation between plasma and intracellular pH awaits clarification. A plausible theory is based on the difficulty with which both the ionic and nonionic contrast media penetrate the RBC membrane (2). Accordingly, these compounds would create diffusion potentials causing a net loss of anions, such as chloride and hydroxyl ion, from the RBCs. This would result in the equivalent loss of hydrogen ions into the plasma and an increase in intracellular pH, leading to a shift of the oxyhemoglobin dissociation curve to the left. The loss of hydrogen ions from the RBCs via the above mechanism would also prevent or significantly attenuate the decrease in intracellular pH following a decrease in plasma pH, which would tend to stabilize P_{50} at the reduced value.

The decrease in P_{50} in blood samples obtained during injection of the contrast media into patients was greater than that observed in our in vitro studies. Although the concentration of contrast media was not measured in the in vivo studies, the greater decrease in hematocrit in these studies suggests that a higher concentration of the medium in vivo was responsible for the accentuated effect (2). It is noteworthy that the adverse effect of the contrast medium in vivo was relatively short-lived; 2 min after injection of the Isovue-370, the oxyhemoglobin characteristics of RBCs had returned to control. This apparently reflects dilution of the contrast medium in the blood volume of the patient. A number of factors would be expected to influence the duration of the P_{50} effect in vivo, including the volume of contrast medium injected, the size of the vascular capacity of distribution, and the rate of entry of the contrast medium into the systemic venous return.

This investigation suggests that both ionic and nonionic contrast media may impair unloading of oxygen from hemoglobin in the capillary blood and thus impede the transport of oxygen to the surrounding tissue. The results demonstrating prevention or attenuation of the Bohr effect also have important physiologic implications because this mechanism facilitates oxygen transport to tissue under conditions of need, including increased metabolic rate and ischemia.

The present findings suggest that large volumes of either ionic or nonionic contrast media should be utilized only with caution in patients with preexisting leftward shifts of the oxyhemoglobin dissociation curve, such as neonates with intracardiac shunts or adult smokers with severe coronary artery disease. It has been observed that injection of contrast media may be accompanied by serious complications in some patients (1,7–10). In infants with large left-to-right shunts, congestive heart failure may worsen (10). Neonates with hypoxemia due to transposition of the great arteries or tetralogy of Fallot may develop marked bradycardia or serious arrhythmias (1). Older children with aortic stenosis and compromised coronary circulation may develop electrocardiographic changes suggestive of myocardial ischemia (10). Because anesthesiologists may be involved in management of patients during and after angiographic procedures, it is important that they be aware of the influences of contrast agents on the oxyhemoglobin dissociation curve.

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Unplanned Incidents During Comprehensive Anesthesia Simulation

Abe DeAnda, BS, and David M. Gaba, MD

DEANDA A, GABA DM. Unplanned incidents during comprehensive anesthesia simulation. Anesth Analg 1990; 71:77–82.

In analyzing recordings of first- and second-year residents performing anesthesia in a comprehensive anesthesia simulation environment (CASE 1.2), we noted the occurrence of unplanned incidents. Utilizing a modified critical incident technique, we documented 132 unplanned incidents during 19 simulations (range 3–14, mean 6.947). Ninety-six (73%) of the incidents were considered simple incidents, and 36 (27%) were considered critical incidents. The incidents were classified as either human errors (65.9%), equipment failures (3%), fixation errors (20.5%), or unknown causes (10.6%). Human errors accounted for 87 of the incidents (range 1–12, mean 4.579), fixation errors accounted for 27 of the incidents (range 0–3, mean 1.421), and equipment failures accounted for only four of the incidents (range 0–2, mean 0.211). There was a significant ($P < 0.025$) difference overall between resident groups, although no one class differed significantly from the others. The data confirm that most incidents are due to human error rather than equipment failure, and document fixation errors as a frequent cause of incidents in anesthesia. The data indicate that although most incidents are simple and do not progress into more serious incidents, human error remains ubiquitous, and that formal training and education should include recognition of events and the responses to them, in addition to prevention.

Key Words: EDUCATION, CLINICAL SIMULATION.

Comprehensive simulators have introduced new approaches to the prospective study of critical incidents in anesthesia (1). These methods are useful in studying both the "chain of accident evolution" (2), and the techniques subjects use to avert or recover from problems and incidents (3). Gravenstein points out that "simulators and training devices have much to offer: the patient is spared, yet student and instructor can explore in detail the sequence of events that may lead to disaster. Simultaneously, simulators enable them to study signs and symptoms of impending problems, as well as different therapies designed to prevent a debacle" (4).

Our previous study using a comprehensive anesthesia simulator investigated the problem-solving techniques used by residents in dealing with critical incidents (3). In this study, residents induced and maintained anesthesia for a "routine" head and neck surgery case, and were challenged with six different events, ranging in severity from a kinked intravenous (IV) tube to a cardiac arrest. In the course of analyzing the responses to these events, we also observed errors or problems that were not directly tied to the planned incidents. We believed that these events were spontaneous and could provide information on the frequency of anesthetic mishaps. Using a modified critical incident technique similar to that used by Cooper and others (5–7), we determined the frequency and nature of these unplanned incidents.

Methods

We have previously described our simulation system (CASE 1.2) in detail (1). Briefly, CASE 1.2 makes use of real monitors, in a real operating room. Waveforms and patient information are provided to the monitors by off-the-shelf and custom simulators. An intubation/thorax mannequin is used as the patient and includes an arm with palpable veins for intravenous

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access. The simulator is controlled from a central computer, with inputs to the monitors being predetermined from a script and altered in real time by the simulator operator. This technique has previously been judged to be highly realistic (3). Subjects were asked to "think aloud" as they worked to provide additional information regarding their actions and responses. An important feature of the CASE 1.2 environment is the use of a videocamera to tape both the simulation and the debriefing session that immediately followed.

Data for this study were collected from videotapes of 19 simulations performed at the Palo Alto Veterans Administration Hospital. The subject of the studies were residents (10 R1, mean experience = 6.6 ± 4.9 wk; 9 R2, mean experience = 74 ± 12 wk) from the Anesthesia Department of Stanford University School of Medicine.

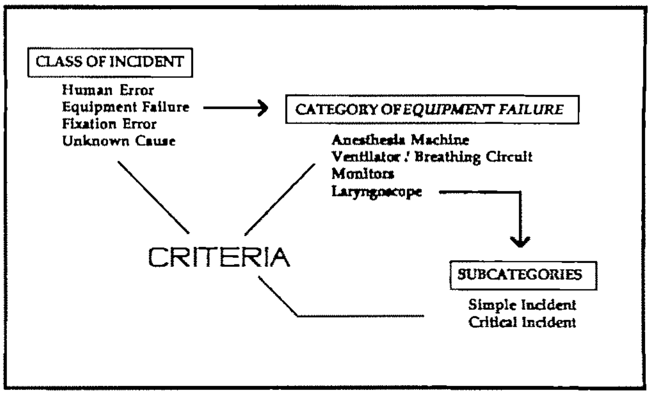

Figure 1. Simplified schematic of the modified critical incident technique. In this example, the categories and subcategories for equipment failures are shown. Classification criteria are utilized at each stage.

DRUG ADMINISTRATION ERRORS

HDA1: SYRINGE / AMPULE SWAP
Simple: Subject recognizes need for correct drug, but draws up wrong drug, AND recognizes error before giving drug.
Critical: Subject has correct drug drawn up but prepares to give wrong drug, OR gives wrong drug but recognizes mistake after giving drug, OR gives wrong drug but never recognizes mistake.

HDA2: WRONG DRUG
Simple: Subject recognizes pathology but chooses wrong drug to treat it, without giving actual drug, OR subject misidentifies pathology but chooses correct treatment modality for treatment of wrong pathology.
Critical: Subject recognizes pathology but chooses wrong drug to treat it, AND administers drug.

Figure 2. An example of the critical incident criteria. In this example, two different drug administration error categories are shown, further subdivided into simple and critical incidents.

Modified Critical Incident Technique

We defined four *classes* of incidents: human errors, equipment failures, unknown causes, and a separate class of human errors—fixation errors. Human errors were either *slips*, "an action (or lack of action) by the anesthesiologist that did not occur as planned" (8), or *mistakes*, "a decision resulting in an action or lack of action by the anesthesiologist that is causally linked to a possible or actual adverse outcome" (8). Fixation errors (8–10) occurred when anesthesiologists were unable to focus on the most critical problem due to "persistent and incorrect fixation of attention and resources" (8). Although fixation errors are a type of human error, we chose to consider them *separately* because they had not been previously addressed in earlier studies. Those incidents in which the etiology could not be clearly demonstrated were labeled as cause unknown. Each class was further subdivided into separate categories using a scheme similar to that used by Cooper et al. (Figure 1) (5).

The class of fixation errors was divided into two categories: physiologic fixation errors and monitor fixation errors. Physiologic fixations occurred when the subject misinterpreted or became fixated on one or more physiologic variables. Monitor fixations occurred when the subject became fixated on a single monitor display, or misunderstood the significance of data from a particular display and thus misinterpreted presented data. This differed from monitor usage errors, a category of human errors that included man-machine interaction errors (such as inadvertently turning off a monitor).

Each category was subdivided into groupings of simple and critical incidents. Simple incidents were those in which a deviation of minimal immediate significance occurred (2), and critical incidents were as defined by Cooper: "an event that could have led (if not discovered or corrected in time) or did lead to an undesirable outcome" (5). Criteria were developed for each of these subcategories (Figure 2).

An example of the use of these criteria is illustrated within the category of fluid management: although the replacement of an IV bag during the course of an operation is a routine and frequent occurrence, we considered this action to be a simple incident if the subject was required to change the bag during a critical event (e.g., cardiac resuscitation), because this took the subject's attention away from the patient. If the subject failed to recognize the bag was empty during a critical period and/or administered IV drugs without recognizing this problem, this was considered to be a critical incident.

Some categories used in previous studies were

Table 1. Total Incidents

Classification	*n* (%)	R1	R2	*P*
Human error	87 (65.9)	57	30	NS
Equipment failure	4 (3.0)	4	0	NS
Fixation error	27 (20.5)	12	15	NS
Unknown cause	14 (10.6)	6	8	NS
Total	132	79	53	

R1, first-year anesthesia residents; R2, second-year anesthesia residents; NS, not significant.
$G = 9.53$, $df = 3$.
$P < 0.025$.

excluded as being inappropriate to our simulation environment. For example, planned but premature extubation was excluded both because the mannequin used in CASE 1.2 is incapable of spontaneous ventilation and the simulations were halted before the emergence stage of anesthesia. Inadvertent extubations *were* included. Hypo/hypervolemia was excluded, because CASE 1.2 does not use a model of fluid balance, and therefore volume status cannot be reliably assessed. In addition, errors directly attributed to artifacts of the simulator were disregarded, including actions secondary to incorrectly generated monitor information and inadequate breath sounds caused by a mechanical failure in the respiratory system of the mannequin.

The resulting data were stratified by the resident groups (R1 and R2) for statistical analysis. The R × C test of independence (11) was used for comparison of the distribution of each category, and an unpaired, two-tailed Student's *t*-test was used for comparisons within each category. Significance was considered at $P < 0.05$.

Results

We documented 132 unplanned incidents during 19 simulations, or 6.9 incidents per case. Of the 132 incidents, 96 were considered simple incidents and 36 were considered critical by our criteria. Overall, the distribution of incidents between resident groups varied significantly ($P < 0.025$) as shown in Table 1. The *t*-test comparing *each class* of incident did not reveal a significant difference in the rate of occurrence between R1 and R2 (although human errors tended toward significance, with $P = 0.0621$).

Human Errors

The distribution of human errors (excluding fixation errors) is shown in Table 2. Ventilator management errors included failure to switch the ventilator power back on after hand-ventilating the patient. Drug administration errors included one ampule swap (where the subject drew up and injected ephedrine rather than epinephrine), as well as failure to physically administer a desired drug. The one anesthesia machine usage error involved the placement of a mask on the "patient's" face for preoxygenation without realizing, for a significant length of time, that the oxygen had not been turned on. The most frequent airway management problems were failure to inflate the endotracheal tube cuff, failure to successfully intubate the trachea, and unplanned endobronchial intubation. Intravenous apparatus errors included inadvertent cessation of IV fluid secondary to an incorrect stopcock setting. Fluid management errors were principally failure to insure a functional IV line when administering IV medications. The largest category of human error was monitor usage error—mostly man-machine interaction errors such as inadvertently turning a monitor off, or turning off the wrong alarm.

Table 2. Human Errors

Category	*n* (%)	R1	R2	*P*
Ventilator/circuit	11 (12.6)	4	7	NS
Drug administration	8 (10.3)	5	3	NS
Anesthesia machine	1 (0.1)	1	0	NS
Airway management	15 (17.2)	11	3	NS
IV apparatus	8 (9.2)	6	2	NS
Fluid management	6 (6.9)	2	4	NS
Monitor usage	32 (36.8)	23	10	0.0325
Other	6 (6.9)	5	1	NS
Total	87	57	30	

$G = 10.01$, $df = 7$. P = NS.
Abbreviations as in Table 1.

An analysis of the distribution of human errors as a whole did not reveal any significant difference between R1 and R2. However, the absolute rate of occurrence of monitor usage errors between R1 and R2 was significant ($P = 0.0325$).

Equipment Failures

Table 3 illustrates the distribution of equipment failures. These included a nonfunctioning laryngoscope light (which had been satisfactorily checked before use) and an O_2 flush valve that stuck open. Equipment failures accounted for the smallest class of incidents, with all the equipment failures occurring with the R1 group. However, the total sample size was insufficient for statistical analysis.

Table 3. Equipment Failures

Category	*n* (%)	R1	R2	*P*
Breathing circuit	2 (50.0)	2	0	NS
Laryngoscope	2 (50.0)	2	0	NS
Total	4	4	0	

Abbreviations as in Table 1.

Table 4. Fixation Errors

Category	*n* (%)	R1	R2	*P*
Physiologic	11 (40.7)	4	7	NS
Monitor data	16 (50.0)	8	8	NS
Total	27	12	15	

G = 0.49, df = 2. *P* = NS.
Abbreviations as in Table 1.

Fixation Errors

Table 4 illustrates the distribution of fixation errors. The most frequent fixation was with monitor displays, with the subjects persistently misinterpreting artifact for patient data, or vice versa. An example of a physiologic fixation error that occurred more than once was in the evaluation of hypotension during an episode of atrial fibrillation. During this episode, blood loss as the *sole etiology* of hypotension was persistently pursued, despite assurances from the "surgeon" that the patient was not bleeding, and electrocardiogram and arterial blood pressure waveform tracings clearly demonstrating atrial fibrillation. The rate and distribution of fixation errors were not significantly different between R1 and R2.

Discussion

These data document incidental failures or errors occurring when trainees managed simulated patients. They confirm the suggestion (2) that simple incidents are not uncommon and that they are often, but not always, handled quickly and appropriately. Such incidents are to be expected if the simulation environment is realistic, with the measured rate of occurrence approaching the field incidence rate as the simulator becomes more realistic. The data also confirm the overwhelming preponderance of human errors rather than frank equipment failures in the observed incident spectrum.

Finally, the data point out the usefulness of this method of investigating critical incidents in anesthesia, a method that has been used by the airline and nuclear power industries to note the occurrence of unplanned incidents during flight and nuclear power plant simulation, respectively (12,13). But is simulation an appropriate way to look for errors and failures? And how do our results compare with those obtained in field studies?

Biases of the Study

There are several potential biases in this study. First, there could be an increased likelihood of errors occurring because of the simulation environment. The time compression associated with our simulation (six planned events in 60–80 min) and the expectation on the part of the subject of adverse events during simulation may create an increase in the subject's anxiety level or cause the subject to be hypervigilant. The former could increase the likelihood of slips and mistakes, the latter might increase the likelihood of fixation errors. However, we noted 87 human errors in 19 cases, or 4.6 human errors per case, the majority of them simple rather than critical incidents. This is similar to the 3.1 to 4.7 human errors per case noted by Holland in his retrospective study of anesthetic mishaps in Australia (14) (this particular study did not measure equipment failures or fixation errors, so these are excluded for this comparison).

It is interesting that Holland's data were elicited from a group of cases where an untoward event was known to have occurred, as was true with our study. However, the human errors identified by Holland were believed to be directly involved in the etiology of the anesthetic mishap, with most of the incidents described being critical incidents. In our study, only 27% were critical incidents. This emphasizes that it may not be the number of incidents that has a bearing on outcome, but the "complexity of interactions" (2) and "tightness of coupling" (2) between the events. The same event may be a simple incident or a critical incident, depending on its relationship with previous or on-going events.

Another potential bias is observer bias: the investigator who categorized the data operated the simulator during the data acquisition. However, because in the initial review of the simulation records we were not attempting to document unplanned incidents but rather focused on the planned incidents, it was required that the tapes be reanalyzed 9–15 mo following simulation, after the criteria had been developed. In developing the criteria, the major categories of errors/failures were taken from other investigators (5,6,9). Thus, the observer bias is negligible and

Table 5. Comparison With Previous Studies

	Cooper '78	Cooper '84	Cooper '84	DeAnda '89
Classification	% (n)	% (n)	% (n)	% (n)
Human error	82 (293)	83 (510)	77 (184)	66 (87)
Equipment failures	14 (50)	11 (69)	19 (46)	3 (4)
Fixation errors	—	—	—	20 (27)
Unknown causes	4 (16)	6 (37)	4 (9)	11 (14)

primarily reflects whatever subjective bias exists within the criteria.

Comparison With Field Studies

A critical difference between the simulator and the real world is that we could identify incidents that might otherwise have been missed. Table 5 compares previous studies with our results. The 1978 study by Cooper et al. used a modified critical incident technique in interviews with anesthesia providers to document 359 preventable incidents, 82% of which were attributable to human error (5). Not surprisingly, Cooper viewed the incidents retrieved from each interview as only a sample representation of an unknown fraction of those actually experienced by the interviewee, with the possibility that self-reporting biased the results to those incidents that were especially memorable to the interviewee. The larger follow-up study in 1984 by Cooper et al. (6) noted overall patterns similar to the earlier results, and included the prospective study technique of "instant-reporting" by independent observers. Cooper reported no significant difference in overall outcome between the retrospective and prospective study techniques. It is notable that of the 359 incidents Cooper documented, 298 were considered to have only transient or minimal effects. Thus, it was possible that because of individual variation in reporting threshold, some subjects overlooked incidents that were easily handled, were considered to be "routine occurrences" rather than incidents, or were hidden and did not progress to a more obvious incident.

There is little doubt that the recording technique used during simulation is sensitive in identifying simple and critical incidents. The use of videotaping, "think aloud" techniques, and debriefing sessions allow an increase in the amount of information collected from each case. Such records avoid the biases associated with self-reporting or retrospective studies and are limited only by the scope of the criteria developed by individual investigators. It would be interesting to apply such techniques to real operations.

How "small" an event constitutes an incident? "Slips" should be regarded as errors regardless of the outcome, because by definition they are events that the anesthesiologist recognizes as actions or inactions that do not occur as planned. For "mistakes," the threshold for the detection of an event becomes more dependent on the specified criteria because the recognition of a "mistake" requires some degree of subjectivity. Presumably, the more subjective and extensive the criteria, the more likely that the criteria will detect a "small" event. The smaller the event, the lower the probability that the event will progress to a critical incident. Thus, we recognize that not all events will lead to a simple incident, and certainly not all will lead to a critical incident.

Nonetheless, although most incidents do not cause harm to the patient, the risk of injury from one event or a combination of events is still real. Only appropriate evaluation and action by the anesthesiologist prevented catastrophe in a number of events we observed. As in previous studies, we noted that most incidents were related to human error, with equipment failures making up only a small fraction of the total number of incidents. Our data document that human error is ubiquitous, at least for trainees. We believe it is likely that similar results will be obtained from experienced faculty and practitioners. Training anesthesiologists to *recognize* and *correct* such events is of equal or greater importance to attempting to prevent the events in the first place.

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Cromolyn Sodium Does Not Inhibit Hypoxic Pulmonary Vasoconstriction in Sheep

Ronald G. Pearl, PhD, MD

PEARL RG. Cromolyn sodium does not inhibit hypoxic pulmonary vasoconstriction in sheep. Anesth Analg 1990; 71:83–7.

Cromolyn sodium has been reported to inhibit hypoxic pulmonary vasoconstriction (HPV) in dogs and sheep, presumably by stabilizing mast cell membranes and thereby preventing the release of mediators such as leukotrienes. Because the effects of leukotriene synthesis and receptor blockers on HPV have been variable across studies, we studied the effect of cromolyn on HPV in the halothane-anesthetized sheep, a model in which we have found leukotriene synthesis and receptor blockers to be ineffective. In control animals, hypoxia (F_{IO_2} = 0.13) increased pulmonary artery pressure ($\bar{P}pa$) 67% and pulmonary vascular resistance 85%, and these responses were reproducible with a second episode of hypoxia. In a second group of sheep, hypoxia (F_{IO_2} = 0.13) during cromolyn administration (6 $mg \cdot kg^{-1} \cdot min^{-1}$) for 30 min increased ($\bar{P}pa$) 104% and increased pulmonary vascular resistance 124%. In a third group of sheep, cromolyn sodium (6 $mg \cdot kg^{-1} \cdot min^{-1}$) without hypoxia did not significantly affect pulmonary hemodynamics. We conclude that cromolyn sodium does not inhibit HPV in halothane-anesthetized sheep. In experimental designs in which cromolyn does alter HPV, the effect is more likely due to altered release of modulators of HPV rather than to decreased release of an obligatory mediator of HPV.

Key Words: LUNG, HYPOXIC VASOCONSTRICTION—cromolyn. PHARMACOLOGY, CROMOLYN.

Hypoxic pulmonary vasoconstriction (HPV) was originally described in the cat as a global pulmonary pressor response to hypoxia (1). Since this original description by von Euler and Liljestrand in 1946, HPV has been extensively investigated in many species (2,3). The mechanisms of HPV, however, remain unknown. Based on inhibition of HPV by leukotriene synthesis inhibitors and receptor blockers in some studies, it has been proposed that leukotrienes may mediate HPV (4–10). However, failure to inhibit HPV with similar or identical agents in other studies has raised questions about the role of leukotrienes as mediators of HPV (11–16). Cromolyn sodium inhibits the release of mediators from mast cells and has therefore been used clinically in the treatment of asthma and other allergic disorders. Cromolyn sodium has been reported to inhibit HPV in dogs and sheep (11,17–22), presumably by stabilizing the mast cell membrane and preventing the release of leukotrienes (17,23). To further define the role of leukotrienes in HPV, we investigated the effects of cromolyn sodium on HPV in the intact halothane-anesthetized sheep.

Methods

The protocol for this study was approved by the Stanford Panel on Laboratory Animal Care.

After an overnight fast, 21 male sheep weighing 14–30 kg were anesthetized with 15–20 mg/kg thiopental intravenously. Sheep were intubated with a cuffed endotracheal tube and mechanically ventilated at a tidal volume of 15 mL/kg and at a rate adjusted to maintain arterial carbon dioxide tension between 35 and 45 mm Hg. Anesthesia was maintained with halothane (end-tidal 1%) throughout the study. After induction of anesthesia, systemic arterial, central venous, and triple-lumen pulmonary artery catheters were inserted by peripheral cutdown. After stabilization for an additional hour, initial baseline measurements during ventilation with halothane in oxygen (F_{IO_2} = 0.99) were obtained. Measured variables included heart rate, mean systemic arterial pressure, mean pulmonary arterial pressure ($\bar{P}pa$), pulmonary

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Table 1. F_{IO_2} and Cromolyn Administration for the Three Experimental Groups

	F_{IO_2}				
	Baseline 1	Hypoxia 1	Baseline 2	Cromolyn 15	Hypoxia 2
Group 1 (control) (n = 7)	0.99	0.13	0.99	— (Untreated)	0.13 (Untreated)
Group 2 (cromolyn) (n = 7)	0.99	0.13	0.99	0.99 (Cromolyn)	0.13 (Cromolyn)
Group 3 (cromolyn control) (n = 7)	0.99	0.13	0.99	0.99 (Cromolyn)	0.99 (Cromolyn)

artery occlusion pressure ($\bar{P}pao$), cardiac output ($\dot{Q}$), and arterial blood gas tensions (Pa_{O_2}, Pa_{CO_2}) and pH.

The experimental protocol is summarized in Table 1. After baseline measurements, hypoxia was induced by reducing the inspired oxygen concentration (F_{IO_2}) to 0.13 using a calibrated gas mixture of oxygen, nitrogen, and 1% halothane; F_{IO_2} was confirmed by direct measurement of inspired gas P_{O_2} (98–100 mm Hg) in each animal. Hemodynamic and blood gas measurements were obtained after 15 min of this hypoxic challenge (hypoxia 1). The F_{IO_2} was then raised to 0.99, and a second set of baseline measurements (baseline 2) was obtained 1 h later.

After baseline 2 measurements, sheep in groups 2 (n = 7) and 3 (n = 7) were given cromolyn sodium (Sigma) at 6 $mg \cdot kg^{-1} \cdot min^{-1}$ for the next 30 min. Fifteen minutes into the cromolyn infusion, hemodynamic and blood gas measurements were obtained (cromolyn 15). While continuing the cromolyn infusion, hypoxia was induced in group 2 by reducing the F_{IO_2} from 0.99 to 0.13; measurements were obtained after 15 min of hypoxia (hypoxia 2). In group 3 animals (n = 7), F_{IO_2} was maintained at 0.99 throughout the cromolyn infusion, and measurements were made after 15 min (cromolyn 15) and 30 min of cromolyn infusion. Group 1 sheep (n = 7) were not treated with cromolyn. In this group, after baseline 2 measurements F_{IO_2} was reduced to 0.13, and measurements were obtained 15 min later (hypoxia 2). As illustrated in Table 1, all three experimental groups have identical treatment at baseline 1, hypoxia 1, and baseline 2 time points. Group 2 demonstrates the effects of cromolyn administration on HPV. Group 1 serves as a control group for the effects of a second hypoxic challenge, and group 3 serves as a control group for the effects of cromolyn without hypoxia.

Measurement Techniques

Intravascular pressures were measured at end-expiration with disposable transducers (Trantec 2000) referenced to left atrial level and recorded on a Hewlett-Packard eight-channel stripchart recorder. Heart rate was measured by continuous electrocardiographic monitoring. Cardiac output was determined in triplicate by thermodilution technique using 10 mL of room temperature saline injectate and an Edwards 9520A cardiac output computer. Blood gas tensions and pH were analyzed using a Corning 168 pH/blood gas analyzer. End-tidal halothane concentration was measured with a Puritan-Bennett Anesthetic Agent Monitor. Pulmonary vascular resistance (PVR) was calculated as ($\bar{P}pa - \bar{P}pao$) × 80/$\dot{Q}$.

Statistical Analysis

Data are expressed as mean ± SEM. Data for each treatment group are analyzed by repeated measures analysis of variance followed by the Newman-Keuls' multiple range test when appropriate (24). Data at each time point are analyzed by one-way analysis of variance followed by the Newman-Keuls' multiple range test when appropriate. A probability value less than 0.05 was considered significant.

Results

There were no significant differences in initial (baseline 1) hemodynamic variables or arterial blood gas values among the three experimental groups (Tables 2 and 3). The initial hypoxic challenge (hypoxia 1) increased $\bar{P}pa$ and PVR equally in all three groups and did not significantly affect any other hemodynamic variable. Overall, hypoxia increased $\bar{P}pa$ 67% and PVR 85%. Pulmonary hemodynamics during hypoxia 1 did not significantly differ among the three groups. Hemodynamics after recovery from hypoxia (baseline 2) were similar to initial baseline 1 values.

In the control group (group 1), a second hypoxic challenge (hypoxia 2) resulted in increases in $\bar{P}pa$ and PVR similar to the first hypoxic challenge (69% and

Table 2. Hemodynamic Effects of Cromolyn Treatment and Hypoxia

	Baseline 1	Hypoxia 1	Baseline 2	Cromolyn 15	Hypoxia 2
PVR (dyne·s·cm^{-5})					
Group 1 (control)	209 ± 54	394 ± 101^a	244 ± 57	—	395 ± 92^a
Group 2 (cromolyn)	141 ± 23	299 ± 51^a	173 ± 21	218 ± 45	488 ± 90^{a,b}
Group 3 (cromolyn control)	240 ± 65	401 ± 107^a	243 ± 46	275 ± 39	321 ± 51
$\bar{P}$pa (mm Hg)					
Group 1 (control)	8.6 ± 1.1	14.7 ± 2.9^a	9.3 ± 1.3	—	15.7 ± 2.4^a
Group 2 (cromolyn)	9.2 ± 1.0	14.6 ± 2.7^a	9.6 ± 0.9	11.2 ± 1.2	22.8 ± 3.2^{a,b}
Group 3 (cromolyn control)	9.0 ± 1.2	15.4 ± 2.4^a	10.6 ± 1.1	11.4 ± 1.3	14.1 ± 2.2
$\bar{P}$pao (mm Hg)					
Group 1 (control)	2.3 ± 1.1	2.1 ± 1.2	1.9 ± 1.0	—	3.1 ± 1.2
Group 2 (cromolyn)	3.8 ± 0.2	3.8 ± 0.2	2.6 ± 0.8	3.0 ± 0.7	3.2 ± 0.6
Group 3 (cromolyn control)	1.6 ± 0.8	2.6 ± 0.8	2.3 ± 0.7	2.6 ± 0.7	2.6 ± 0.8
$\bar{P}$sa (mm Hg)					
Group 1 (control)	90 ± 8	92 ± 9	95 ± 11	—	86 ± 13
Group 2 (cromolyn)	89 ± 6	91 ± 3	92 ± 4	91 ± 6	87 ± 4
Group 3 (cromolyn control)	88 ± 10	82 ± 10	86 ± 12	81 ± 7	84 ± 8
$\dot{Q}$ (L/min)					
Group 1 (control)	2.61 ± 0.21	2.71 ± 0.27	2.68 ± 0.29	—	2.82 ± 0.35
Group 2 (cromolyn)	2.64 ± 0.21	2.86 ± 0.25	2.69 ± 0.08	2.80 ± 0.11	3.13 ± 0.16
Group 3 (cromolyn control)	2.63 ± 0.30	2.67 ± 0.34	2.58 ± 0.26	2.42 ± 0.17	2.59 ± 0.20
HR (beats/min)					
Group 1 (control)	117 ± 12	131 ± 15	129 ± 8	—	147 ± 13
Group 2 (cromolyn)	95 ± 8	112 ± 10	102 ± 8	96 ± 10	113 ± 9
Group 3 (cromolyn control)	118 ± 7	134 ± 12	129 ± 12	121 ± 15	120 ± 13

PVR pulmonary vascular resistance; $\bar{P}$pa, mean pulmonary artery pressure; $\bar{P}$pao, pulmonary artery occlusion pressure; $\bar{P}$sa, mean systemic arterial pressure; $\dot{Q}$, cardiac output; HR, heart rate.

Values are mean ± SEM.

^{a}$P < 0.01$ compared with corresponding baseline value.

^{b}$P < 0.01$ compared with cromolyn 15 value.

Table 3. Arterial Blood Gas Tensions and pH

	Baseline 1	Hypoxia 1	Baseline 2	Cromolyn 15	Hypoxia 2
pH (units)					
Group 1 (control)	7.39 ± 0.04	7.43 ± 0.06	7.40 ± 0.05	—	7.43 ± 0.03
Group 2 (cromolyn)	7.39 ± 0.02	7.44 ± 0.02	7.38 ± 0.02	7.41 ± 0.01	7.42 ± 0.01
Group 3 (cromolyn control)	7.41 ± 0.02	7.44 ± 0.01	7.41 ± 0.01	7.40 ± 0.01	7.41 ± 0.01
Pa_{O_2}					
Group 1 (control)	494 ± 22	43 ± 2^a	489 ± 28	—	42 ± 2^a
Group 2 (cromolyn)	502 ± 23	44 ± 3^a	497 ± 17	515 ± 17	42 ± 2^{a,b}
Group 3 (cromolyn control)	480 ± 24	42 ± 2^a	465 ± 39	481 ± 45	442 ± 56
Pa_{CO_2} (mm Hg)					
Group 1 (control)	38 ± 2	38 ± 2	40 ± 2	—	38 ± 1
Group 2 (cromolyn)	37 ± 1	35 ± 1	40 ± 1	38 ± 1	37 ± 1
Group 3 (cromolyn control)	39 ± 2	38 ± 2	39 ± 3	40 ± 2	37 ± 3

Values are mean ± SEM.

^{a}$P < 0.01$ compared with corresponding baseline value.

^{b}$P < 0.01$ compared with cromolyn 15 value.

61%, respectively). In the two cromolyn groups (2 and 3), cromolyn administration for 15 min with $F_{IO_2} = 0.99$ did not significantly affect any hemodynamic variable. In group 2, hypoxic challenge during cromolyn administration resulted in large increases in $\bar{P}$pa and PVR (104% and 124%, respectively, compared to cromolyn 15 values). In group 3, cromolyn administration for 30 min resulted in small nonsignificant increases in $\bar{P}$pa and PVR. The increases in $\bar{P}$pa and PVR attributable to hypoxic challenge in the cromolyn group (i.e., the differences between group 2 and group 3 at hypoxia 2) were similar to the effects of initial hypoxic challenge in the cromolyn group.

Discussion

The current study demonstrated that intravenous cromolyn sodium did not decrease the pulmonary pressor response to hypoxia in halothane-anesthetized male sheep. These results differ from other studies using conscious ewes (17) and 9–11-day-old conscious lambs (18). Although we did not assess inhibition of mast cell degranulation, we used a dose twice that used in the other studies with sheep and still were unable to inhibit HPV. As discussed below, the differences in results are best explained by differences in experimental design interacting with possible modulators of the pulmonary pressor response.

The mechanisms of HPV have been extensively investigated over the past four decades. Several lines of evidence have suggested that HPV may be dependent on mast cell release of mediators such as the leukotrienes. Lloyd (25) demonstrated that perivascular tissue is required for hypoxia-induced contraction of pulmonary artery strips. Haas and Bergofsky (26) demonstrated that perivascular mast cells in the rat lung degranulate during hypoxia. Cromolyn sodium stabilizes the mast cell membrane (23) and prevents the hypoxic degranulation of mast cells (17). Cromolyn sodium prevents the pulmonary pressor response to hypoxia in sheep (17,18) and dogs (11,19,20); aerosolized cromolyn has also been effective in sheep (21,22). Cromolyn does not appear to alter the pulmonary pressor response to norepinephrine, tyramine, or histamine (17), suggesting that the decreased hypoxic response is due to decreased release of mediators rather than to decreased sensitivity of the pulmonary vasculature. Cromolyn does decrease hypoxia-induced release of histamine from guinea pig lung (27) but histamine does not appear to be an obligatory mediator for hypoxic pulmonary vasoconstriction (17,28). The slow-reacting substance of anaphylaxis (SRS-A) is a mixture of leukotrienes (29) released during antigenic stimulation that is capable of producing contraction of pulmonary vascular smooth muscle (30). Pulmonary leukotriene release occurs during hypoxia (31) and leukotriene synthesis inhibitors and receptor antagonists can prevent hypoxic pulmonary vasoconstriction (4–10).

The above evidence suggests that hypoxic pulmonary vasoconstriction may depend on mast cell release of leukotrienes. However, if this mechanism is *the* mediator of HPV rather than a modulator of HPV, it is essential both that leukotriene inhibitors consistently prevent HPV and that cromolyn consistently prevents HPV. Although early reports consistently demonstrated inhibition of HPV by leukotriene synthesis inhibitors and receptor antagonists, more recent studies have frequently been unable to inhibit HPV with similar agents (11–16).

A critical review of the literature on the effects of cromolyn on HPV similarly demonstrates ambiguity. In the first report of the effect of cromolyn on HPV, Kay and Grover (20) noted variable effects—cromolyn abolished HPV in three dogs but had no effect on HPV in five other dogs. Rengo et al. (19) reported that although cromolyn inhibited the pressor response to hypoxia, this inhibition was related to the cromolyn-induced increase in vagal tone so that after atropine pretreatment cromolyn was ineffective in preventing HPV. Howard et al. (32) reported no effect of cromolyn on HPV in a perfused in vivo dog lung lobe preparation, and Porcelli et al. (33) reported no effect in the isolated perfused feline pulmonary circulation. Similar to our study, Frantz et al. (34) reported that cromolyn did not alter hypoxia-induced pulmonary hypertension in newborn and young lambs. In an abstract, Hallemans et al. (35) reported failure of cromolyn to inhibit HPV in humans. The relationship between mast cell degranulation and HPV has also been questioned. Mast cell-deficient mice develop pulmonary hypertension during chronic hypoxic exposure (36) and the pulmonary pressor response is inversely related to mast cell density in cats treated with radiation and nitrogen mustard (37).

Studies investigating the effects of cromolyn on HPV have differed in the dose of cromolyn used and the choice of species, gender, age, model, timing of hypoxia, and the use of anesthesia. Each of these variables may affect the HPV response (38–42). Although none of these variables are by themselves sufficient to explain the differences among studies, the multiple positive and negative reports are most consistent with the hypothesis that cromolyn does not inhibit release of *the* mediator of HPV but may inhibit release of one or more modulators of HPV and that the importance of such modulators may vary with differences in experimental design. A modulatory role has been demonstrated for histamine (37,43) and for the sympathetic nervous system (44). Ahmed and Marchette (45) have demonstrated that hypoxia enhances bronchial reactivity to aerosolized histamine and carbachol and that this enhanced reactivity is prevented by pretreatment with cromolyn.

In summary, in the present study cromolyn sodium did not alter the pulmonary pressor response to hypoxia in halothane-anesthetized sheep, suggesting that mast cell degranulation and concomitant release of leukotrienes are not obligatory for hypoxic pulmonary vasoconstriction. Our results do not rule out a possible modulating effect on HPV of mast cell degranulation and leukotriene release.

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Clinical Reports

Electrocardiographic Artifacts During Cardiopulmonary Bypass

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Key Words: ANESTHESIA, CARDIOVASCULAR—ECG interference. MONITORING, ELECTROCARDIOGRAPHY—interference.

> You see what you look for, you look for what you know.
>
> Goethe

An electrocardiogram (ECG) free from interference is today a necessity for safe anesthetic management. Electrocardiogram artifacts caused by surgical cautery units, power lines, and muscle twitching and fasciculation have been recognized (1–4). More recently, ECG interference has been observed during extracorporeal shock wave lithotripsy (5) and during crystalloid administration through a fluid warming apparatus (6). During cardiopulmonary bypass (CPB) we have been experiencing another type of ECG artifact, which has not yet been reported. The purpose of this paper is to describe the characteristics and incidence of this interference, and to suggest an etiology and possibly a solution to the problem.

Methods

The ECGs of 82 patients undergoing open heart surgery in two different operating rooms were inspected and recorded with the permission of the Institutional Review Board. All electrical outlets were checked for proper polarity, continuity, contact tension, and grounding. A different Stockert Shiley HLM extracorporeal bypass machine with four variable speed roller heads and Medtronics Cardiopulmonary Products Intersept 2070-1 polyvinyl chloride tubing was used in each operating room. A Maxima membrane oxygenator and a Sorensen heat exchanger were included. All the devices routinely maintained by the manufacturers were checked repeatedly and found to be free of any electrical faults.

One precordial and four limb 3M Red Dot ECG electrodes were applied after the skin was degreased and abraded. The electrodes were inspected to insure that the conductive gel was intact, and the integrity of the ECG lead wires and cable was verified. Clean contact and good mechanical connection were assured between the electrodes and lead wires, and also between the lead wires and the ECG cable. Six standard leads and V_5 were monitored using a Hewlett-Packard 78208A ECG module and 78304A display. Lead V_5 was recorded on a Hewlett-Packard 7758A chart recorder from the beginning of anesthesia to the end of surgery.

The occurrence of ECG artifacts was correlated with ambient relative humidity and temperature in the operating rooms. Relative humidity in the operating room was calculated from measurements made with a battery-powered psychrometer (model 566, Belfort Instrument Co., Baltimore, Md.). Of the 82 patients studied, 52 were monitored in the winter months (December, January, and February) and 30 in the summer months (July, August, and September). When ECG artifacts were observed, the CPB tubing in the roller heads was sprayed with tap water from an atomizer. On two occasions when the artifact persisted following this treatment, polyethylene glycol (Carbowax PEG 600; Union Carbide Corp., Danbury, Conn.) was also sprayed from an atomizer.

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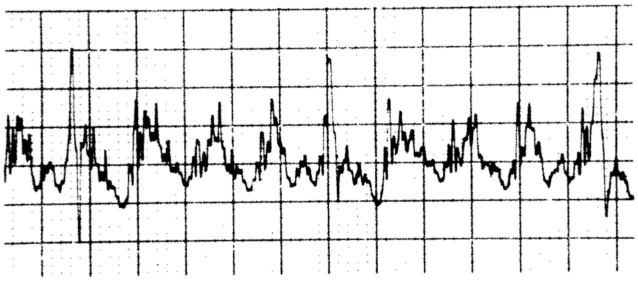

Figure 1. Electrocardiogram interference on initiation of cardiopulmonary bypass.

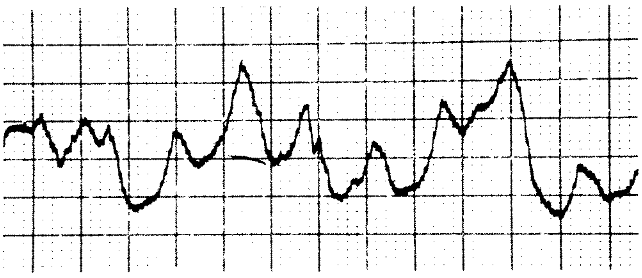

Figure 2. Electrocardiogram interference during cardiopulmonary bypass after rewarming and defibrillation of the heart.

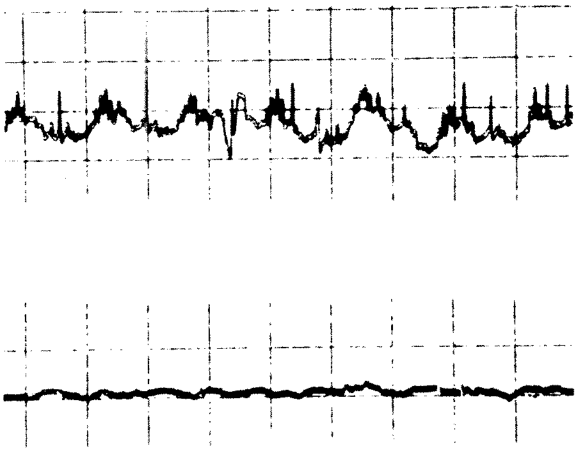

Figure 3. Electrocardiogram interference during cardiopulmonary bypass with cardiac standstill; (*top*) before and after (*bottom*) spraying with water.

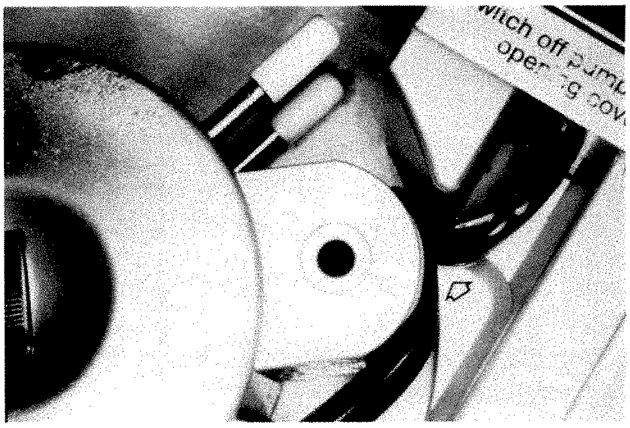

Figure 4. Kinked tubing in the suction roller pump after application of polyethylene glycol to the tubing.

Statistical analysis was obtained using χ^2; $P < 0.05$ was considered significant.

Results

There was no ECG interference in any of the 82 patients until after the onset of CPB. At that time, ECG artifacts developed while the heart was still beating in 28 patients (56%) in the winter group and four patients (13%) in the summer group. This interference, which had a frequency of 1–4 Hz and an amplitude as high as 5 mV peak to peak, sometimes obscured the ECG tracing sufficiently to make interpretation no longer possible (Figure 1). After cardioplegia was given, differentiation from ventricular fibrillation was often impossible, and the ECG could not be relied on to document cardiac standstill. After rewarming and defibrillation, one could not always tell when the patient's own rhythm had returned, and it was difficult to diagnose and treat conduction abnormalities by observing the ECG tracing (Figure 2). Reliance on these occasions had to be placed on direct observation of the heart. In all instances, the ECG artifacts disappeared as soon as CPB was discontinued.

In the winter group, when artifacts were present the relative humidity in the operating rooms was 45% or less (range, 23%–45%; $P < 0.01$) and the temperature was 18°C or less (range, 14°–18°C; $P < 0.01$). In the summer group, when artifacts were present the relative humidity in the operating rooms was 48% or less (range, 42%–48%; $P < 0.05$) and the temperature was 20°C or less (range, 18°–20°C; $P < 0.05$). In 24 of the 32 patients in whom ECG interference developed, spraying tap water on the CPB tubing in the roller pumps improved the quality of the tracing (Figure 3). In two of the cases in which this was unsuccessful, spraying the CPB tubing with polyethylene glycol led to complete disappearance of the artifacts. However, in those two cases the tubing in a suction roller pump kinked 10 min later, and the motor stalled (Figure 4).

Discussion

Electrocardiogram interference during CPB, although unreported heretofore, is not a new phenomenon.

The Norton Company in Akron, Ohio, which was one of the first to produce CPB tubing, has maintained a file of incidents of ECG interference during CPB for the past 10 yr (personal communication from R. Charton, BS, Norton Company, Akron, Ohio). Electrocardiogram interference during CPB is also well-recognized at the Massachusetts General Hospital (MGH) where it occurs as frequently as two to three times per week, a frequency similar to ours. At MGH, spraying the CPB tubing with silicone has proven somewhat helpful (personal communication from Daniel Philbin, MD, and Richard DeCesare, CCE, Massachusetts General Hospital, Boston, Mass.). The persistence of the problem, the absence of a published report, and the need to understand the cause and arrive at a solution prompted us to undertake this systematic inquiry of the incidence and cause of this type of ECG interference. However, when this interference did occur, patient safety was not jeopardized, because on occasions when the ECG could not be interpreted reliance was placed on direct observation of the heart.

There is evidence in the literature connecting mechanical motion and plastic tubing with ECG artifacts. In one report, crystalloid solution infused via plastic tubing placed in the electrical warming unit produced ECG interference, which the authors attributed to static electricity (6). In another report, the authors attributed ECG interference to piezoelectric effect produced by plastic tubing in the infusion pump (7).

Because the ECG interference in our patients occurred during CPB only, we postulate that it was due either to a piezoelectric effect or to static electricity within the CPB tubing. Piezoelectricity is an electrical charge generated by the stress of mechanical deformation on certain types of anisotropic crystals. This effect has been demonstrated in polymer plastics of the polyvinyl fluoride type (8), but not in the polyvinyl chloride used for CPB tubing. However, most polymeric materials have some piezoelectric properties (9), and plasticizers and conditioners that alter plastic base material have piezoelectric effects.

Static electricity is generated when electrons are removed from the atoms on the surface layer of an electrically nonconductive substance, leaving behind a charged surface (10). Plastics, in particular, have a proclivity to generate static electricity, which is typically produced by rapid constant rubbing and separation of dissimilar surface materials (e.g., tubing and pump roller head), at least one of which must be nonconductive. One of the surfaces will gain electrons while the other will lose them. The electrons transferred are those in the outermost orbit of the surface atoms.

During the manufacture of CPB tubing, at linear speeds of 4500 m/h a very high static charge is built up on the plastic surface, and a special step, known as destaticizing, is necessary (personal communication from R. Anderson, Plastron Inc., City of Industry, California). During CPB, with a roller pump of 12.7-cm diameter that is rotating at 3 revolutions per second, the roller head will move over the plastic tubing at a linear speed of approximately 4000 m/h, well within the range in which static electricity can be expected.

Static electricity is more readily generated when atmospheric conditions are cool and dry, when there is little surface moisture present to dissipate electrical charge. Indeed, the ECG artifacts were observed on days when the relative humidity in the operating room was 48% or less and the temperature 20°C or less. As our investigation demonstrates, it is climate control in the operating room that affects the incidence of ECG interference, not outside weather conditions. In fact, when ECG interference occurred ambient conditions in the operating rooms were identical despite seasonal differences in outside weather.

Spraying tap water from an atomizer on the external surface of the CPB tubing was only moderately effective in resolving ECG interference. Improvement occurred in 75% of the patients, and repeated applications were necessary. Local tap water has a conductivity in the order of 70 micromho/cm as compared to 1 micromho/cm for distilled water and 10^4 micromho/cm for normal saline. Polyethylene glycol spray was used on two occasions when water spray was ineffective. Polyethylene glycol is a linear polymer formed by the addition reaction of ethylene oxide. It is used in various manufacturing processes to reduce static electricity. We used a version with an average molecular weight of 600 amu because it is a clear viscous liquid at room temperature. The film of polyethylene glycol, although it did eliminate the ECG interference, caused the tubing used for suctioning to kink and become entangled in the roller pump. This occurred because the suction tubing, being of a smaller diameter than that used for the delivery of arterialized blood, fits rather loosely in the pump and is therefore prone to kinking. It is interesting to note that spraying silicone on the CPB tubing at the MGH was also often effective.

We propose that for the following reasons static electricity rather than a piezoelectric effect was responsible for the observed ECG artifacts: (a) artifacts occurred on days when the ambient air in the operating rooms was cool and dry; (b) improvement was noted by us after spraying tap water on the CPB tubing and by those at MGH when silicone was similarly used; and (c) polyethylene glycol, a known destaticizer, was effective in resolving ECG interference.

One solution to the problem of ECG interference during CPB would be to use electrically conductive and grounded CPB tubing. Such a conductor would offer a low resistance pathway for static charge to dissipate and would effectively short-circuit any generated piezoelectric voltage. The conductive layer should be confined to the outer surface of the tubing in contact with the pump roller heads so that the patient remains ungrounded. It was recently reported that new polymers are being developed (11), ones that possess electrical conductive properties that are expected to eliminate the problem of electrical interference. Their use in CPB tubing manufacturing would eliminate the need for grounding. Until either of these proposed solutions becomes available, more attention should be paid to the operating room environment, and to maintaining the ambient temperature above 20°C and relative humidity above 50%.

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Operative Lung Continuous Positive Airway Pressure to Minimize F_{IO_2} During One-Lung Ventilation

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Key Words: ANESTHESIA, THORACIC—one-lung ventilation. VENTILATION, ONE-LUNG.

Patients undergoing one-lung ventilation have a high risk of developing hypoxemia. Inspired oxygen concentrations (F_{IO_2}) of 1.0 are, therefore, commonly employed during one-lung ventilation to minimize this risk. If hypoxemia does develop during one-lung ventilation, then 5–10 cm H_2O continuous positive airway pressure (CPAP) with oxygen applied to the nonventilated lung is an effective treatment.

Some investigators believe that bleomycin-treated patients are at an increased risk to develop pulmonary complications if exposed to an F_{IO_2} greater than 0.30 (1–8). If a bleomycin-treated patient, or any other patient with pulmonary disease were ventilated with F_{IO_2} less than 0.30 during one-lung ventilation, then the risk of hypoxemia would indeed be great. We herein report the use of nonventilated lung CPAP with an F_{IO_2} of 0.30 to allow a ventilated lung $F_{IO_2} = 0.30$ during one-lung ventilation so that $Pa_{O_2} \geq 79$ mm Hg (which was not possible without nonventilated lung CPAP) in a bleomycin-treated patient undergoing bilateral resection of testicular carcinoma pulmonary metastases. Forethought and special equipment (described herein) are necessary to administer CPAP with a variable F_{IO_2} to the nonventilated lung.

Case Report

The patient, a 30-yr-old man with testicular carcinoma, was admitted for resection of bilateral metastatic pulmonary nodules. Seven years before admission he had undergone right orchidectomy and lymph node dissection for germ cell carcinoma. He did well for approximately 6 yr until he presented with a left testicular mass and pulmonary metastases involving both lungs. After left orchidectomy, the patient received a total cumulative dose of bleomycin of 150 U. After completion of the course of chemotherapy and improvement in tumor markers, the patient was scheduled for resection of bilateral pulmonary nodules via a median sternotomy.

The patient weighed 89 kg and was 175 cm tall; preoperative vital signs included blood pressure 122/76 mm Hg, pulse 85 beats/min, and respiratory rate 12 breaths/min. The patient denied dyspnea, cough, or bronchospastic symptoms. Pulmonary function tests revealed mild expiratory obstruction with FEV_1/FVC 66% of predicted and several forced expiratory flows that were all significantly reduced to 40%–50% of predicted ($FEF_{25\%}$, 4.6 L/s; $FEF_{50\%}$, 2.6 L/s; $FEF_{75\%}$, 0.9 L/s). Diffusing capacity measured with carbon monoxide was decreased to the lower limit of normal value of 22.2 mL $CO \cdot min^{-1} \cdot mm\ Hg^{-1}$. Arterial blood had a pH of 7.43, Pa_{CO_2} 37 mm Hg, and Pa_{O_2} 96 mm Hg while the patient was breathing room air.

Preoperative sedation was accomplished with midazolam (3 mg IV). Intraoperative monitoring included a radial arterial catheter, pulse oximetry, automatic blood pressure, electrocardiogram, temperature, end-tidal CO_2, mass spectrometry, and a polaragraphic oxygen analyzer. Preinduction arterial blood gas tensions are shown in Table 1. Anesthesia was induced with 700 μg IV fentanyl in divided doses, 450 mg IV thiamylal, and inhalation of isoflurane (1.5%–2.0% for several minutes). Tracheobronchial intubation with a 39F left-sided double-lumen tube was facilitated by 10 mg IV vecuronium. Proper placement of the double-lumen tube was confirmed by unilateral clamping maneuvers, auscultation of breath sounds, and fiberoptic bronchoscopy. Anesthesia was maintained with 1.0%–1.5% isoflurane, 250 μg fentanyl, and 6 mg IV vecuronium in divided doses.

During induction of anesthesia, the F_{IO_2} was 0.26–0.28, the pulse oximeter reading (Sp_{O_2}) was always

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Table 1. Arterial Blood Gas Tensions and Fio_2 in Each Lung Before, During, and After One-Lung Ventilation in a Bleomycin-Treated Patient

Time	Fio_2 condition				pH	Pao_2 (mm Hg)	Paco_2 (mm Hg)
	Right lung		Left lung				
1. 0800 (before induction)	Room air	Spontaneous ventilation	Room air	Spontaneous ventilation	7.39	103	39
2. 0859 (chest open)	0.29	IPPV	0.29	IPPV	7.37	133	41
3.* 0937 (chest open)	0	Atelectasis	0.30	IPPV	7.34	48	44
4. 0953 (chest open)	0.38	CPAP 10 cm H_2O	0.30	IPPV	7.32	79	49
5. 1008 (chest open)	0.38	CPAP 10 cm H_2O	0.27	IPPV	7.33	116	44
6. 1100 (chest closed)	0.24	IPPV	0.24	IPPV	7.34	93	44
7. 1115 (chest closed)	0.24	Spontaneous ventilation	0.24	Spontaneous ventilation	7.32	91	43

IPPV, intermittent positive pressure ventilation.

*Arterial blood for measurement of gas tensions was drawn during a time of rapidly decreasing arterial oxygen saturation measured by pulse oximetry (see text for details).

greater than or equal to 95%, and, with a two-lung positive pressure tidal volume of 12 mL/kg and a respiratory rate of 8–10 breaths/min, the end-tidal CO_2 tension was maintained between 37 and 40 mm Hg. With the patient in the supine position, median sternotomy was performed, the left pleural space entered, and two nodules in the left upper lobe resected while two-lung ventilation was continued (surgical visualization was adequate); during this left-lung resection, oxygenation and ventilation were unperturbed (Table 1, second row). The left pleural space was then closed and attention turned to the right lung.

Exploration and resection of the nodules in the right lung required one-lung (left) ventilation. At the initiation of one-lung ventilation, left lung Fio_2 was 0.30, tidal volume 10 mL/kg, respiratory rate 12 breaths/min, and the right lung was open to atmosphere. Within 2 min, Spo_2 decreased precipitously. An arterial blood sample drawn during approximately the midpoint of the Spo_2 descent (Spo_2 = 85%) had a Pao_2 of 48 mm Hg (Table 1, third row). The Spo_2 was 69%, at which point two-lung ventilation (tidal volume 12 mL/kg, respiratory rate 9 breaths/min) was reinstituted, with the Fio_2 maintained at 0.30; the Spo_2 increased to 100% within 2 min.

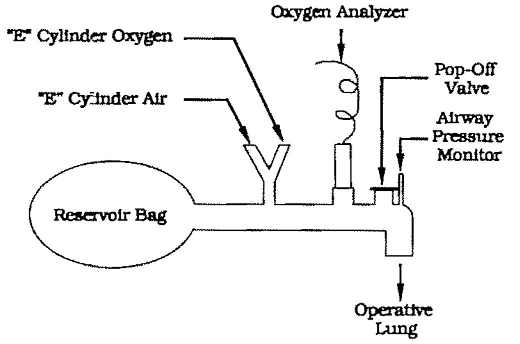

Figure 1. Schematic of the variable Fio_2, operative lung, CPAP system used in our patient. Oxygen and room-air tanks are connected by a Y-piece leading to an Fio_2 analyzer; the Fio_2 analyzer is connected in series to a CPAP device consisting of a reservoir bag with pressure-relief valve and a pressure manometer.

A trial of 10 cm H_2O of right-lung CPAP was undertaken while only the left lung was ventilated (Fio_2 = 0.30, tidal volume = 10 mL/kg, respiratory rate = 12 breaths/min). The right-lung CPAP was applied during the expiratory phase of the last two-lung tidal volume. The CPAP apparatus consisted of a 100% oxygen tank and a room air tank, both with flow meters, joined by a Y-piece, and in series with a rapidly responding Fio_2 analyzer, a pressure manometer, and a reservoir bag with an Heidebrink pressure-relief valve (Figure 1). This system allowed the administration of an Fio_2 between 0.21 (no flow from the oxygen tank) to 1.0 (no flow from the room air tank), and any level of CPAP. Fio_2 for the nonventilated CPAP lung was 0.38 initially (Table 1, row 4). The Fio_2 for the CPAP and nonoperative lung was reduced as tolerated (Table 1, row 5). With this approach, the Pao_2 was maintained between 79 and 116 mm Hg during one-lung (left) ventilation. Excellent surgical visualization was provided. After resection of one right upper lobe and three right lower lobe nodules, two-lung ventilation was reinstituted (parameters as above) and the sternotomy was closed (Table 1, row 6). After sternotomy closure, muscle relaxation was reversed with neostigmine and glycopyrrolate, and the patient was allowed to breathe spontaneously (Table 1, row 7). The trachea was extubated uneventfully. Total fluid volume administration was 1800 mL lactated Ringer's, estimated blood loss was 225 mL, and urine output was 500 mL. The patient had an uneventful postoperative course;

arterial blood gas tensions while breathing room air on the first postoperative day included a pH of 7.35, Pao_2 of 72 mm Hg, and $PaCO_2$ of 38 mm Hg. The patient was discharged on the sixth postoperative day.

Discussion

The relationship between increased, but normally nontoxic, concentrations of oxygen in bleomycin-treated patients and pulmonary fibrosis is controversial. Although there are human and animal data to suggest that the use of elevated oxygen concentrations in bleomycin-treated patients increases the risk of pulmonary damage (1–8), the data from humans fail to establish a cause-and-effect relationship, and the animal data contain experimental design aberrations such as direct administration of bleomycin intratracheally (as opposed to intravenous administration as done clinically). The fact that bleomycin's antitumor activity is dependent on the production of superoxide- and hydroxyl-free radicals, which can selectively damage DNA (9), provides a cellular basis for the contention that elevated Fio_2 and bleomycin may interact in a positive way to produce pulmonary damage. On the other hand, there are both human (10) and animal (11,12) data that equally strongly suggest that increased oxygen concentrations in bleomycin-treated patients do not cause acute pulmonary damage. At the present time, we consider the matter unsettled. Nevertheless, we believe that it is reasonable to minimize the Fio_2 to both the nonoperative and operative lung as long as it is documented that it is safe to do so by measuring Spo_2 and Pao_2.

The risk of hypoxemia due to one-lung ventilation with a restricted Fio_2 is considerable, whereas the benefit to a bleomycin-treated patient, as discussed above, is speculative and theoretical. Thus, the risk-benefit ratio of bleomycin patients undergoing one-lung ventilation with a restricted Fio_2 appears to be high. We think it reasonable to limit the Fio_2 as much as possible as long as the patients are not hypoxemic ($Pao_2 > 70$ mm Hg, $Spo_2 > 90\%$), and the use of pulse oximetry as a continuous monitor is very helpful in this regard.

The best way to limit Fio_2 in patients undergoing one-lung ventilation is to apply CPAP to the nonventilated lung. Applying CPAP to the nonventilated lung simply distends the alveolar space with oxygen-containing gas and thus greatly reduces the shunt flow through the nonventilated lung. The CPAP must be delivered on the deflation phase of a previous breath (to avoid the need to exceed high critical opening pressures), and the level attained should be monitored by an in-line dry gas pressure manometer. Five- to ten-centimeter H_2O CPAP has been found to be just as effective as 15 cm H_2O (13), and because the lower levels of CPAP have less hemodynamic effect, they should be tried first (13). With all considerations being otherwise equal, it should be less necessary to use operative lung CPAP to minimize Fio_2 during one-lung ventilation in the lateral decubitus position than in the supine position due to the relatively diminished amount of blood flow to the operative lung in the lateral decubitus position.

The CPAP system we used allowed a completely variable Fio_2 and CPAP level to be administered to the nonventilated lung. Such flexibility in Fio_2 and CPAP level is highly desirable in a very dynamic situation where the level of oxygenation requires very fine tuning, and can be dramatically affected by many factors at any time. It is possible that more detailed attention to the ventilated lung, in terms of PEEP level, tidal volume, and respiratory rate might also contribute to minimizing the Fio_2 to both lungs.

In summary, we described the use of nonventilated lung CPAP to minimize Fio_2 to both lungs in a bleomycin-treated patient requiring one-lung ventilation. Without the use of nonventilated lung CPAP, the patient became severely hypoxemic during one-lung ventilation. Nonventilated lung CPAP easily restored the arterial Pao_2 back to adequate levels and provided adequate surgical visualization. Based on the results of this case, we think that preoperative preparation should be made to administer nonventilated lung CPAP with a variable Fio_2 with a system similar to the one we used in this case for any patient undergoing one-lung ventilation who requires a restricted Fio_2.

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Anesthetic Management of a Parturient With Osler–Weber–Rendu Syndrome and Rheumatic Heart Disease

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Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—Osler–Weber–Rendu syndrome. COMPLICATIONS, OSLER–WEBER–RENDU SYNDROME.

Osler–Weber–Rendu (OWR) syndrome, or hereditary hemorrhagic telangiectasia, is an autosomal dominant syndrome characterized by an abnormal vascular ultrastructure resulting in telangiectasia, arteriovenous (AV) fistulas, and aneurysms throughout the cardiovascular system (1). It is an uncommon disease with a frequency of 1–2 per 100,000 persons (1). Severe rheumatic heart disease is a well-known sequela of rheumatic fever and, when combined with pregnancy, may account for a maternal mortality of approximately 7% (2). Although a case of OWR syndrome in a parturient with pulmonary AV fistulas and hypoxia has been described (3), no report has considered anesthetic management of a parturient with OWR alone, much less a parturient with both rheumatic heart disease and OWR syndrome. We report the anesthetic management of a laboring patient with both OWR syndrome and severe rheumatic heart disease and suggest a technique for the induction of epidural anesthesia designed to minimize maternal and fetal risk.

Case Report

A 27-yr-old woman (gravida 3, para 2 at 26-wk gestation) presented to the University of Alabama at Birmingham Hospital with a known 2-yr history of OWR syndrome and rheumatic heart disease. In the 4 wk before admission, she had noted progressively worsening dyspnea on exertion and arrived at our hospital with severe hypoxemia (Pa_{O_2} = 35 mm Hg) refractory to mechanically controlled endotracheal ventilation with 100% oxygen. Chest x-ray revealed several large opacities in both lungs and a large collection of fluid in the right pleural space, which was interpreted as a hemothorax secondary to a ruptured pulmonary AV malformation. Thoracocentesis confirmed the hemothorax, and pulmonary angiography revealed several large bilateral AV fistulas, which were subsequently occluded with "coiled spring" embolization. Although several small pulmonary AV fistulas remained, the patient responded well to this therapy. The trachea was extubated, and a Pa_{O_2} of 80 mm Hg was maintained with oxygen by face mask (F_{IO_2} = 0.30).

In the ensuing 6 wk, the patient's hospital course became complicated with worsening dyspnea at rest, hemoptysis, and transudative pleural effusions. Doppler echocardiography revealed massive mitral regurgitation, mild mitral stenosis (mitral valve area = 1.99 cm^2), moderate pulmonary hypertension, right ventricular dilation, and tricuspid regurgitation. The patient was treated with supplemental oxygen, diuretics, afterload reduction, and fluid restriction. Despite aggressive medical therapy her symptoms worsened and induction of labor was deemed necessary at 32-wk gestation.

Three days before the planned induction of labor, the patient was transferred to the medical intensive care unit where a pulmonary artery catheter was inserted with baseline hemodynamic values measured (Table 1). She underwent further diuresis and was given an intravenous infusion of dobutamine at a rate of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for inotropic support, which moderately improved her hemodynamic status (Table 1). An epidural catheter was placed at the L2-3 interspace using an 18-gauge Tuohy–Weiss needle with a saline loss-of-resistance technique. No cerebrospinal fluid or blood was noted in either the needle hub or catheter. A fluid bolus was not administered before the institution of epidural anesthesia. A "test dose" of local anesthetic using a standard

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Table 1. Hemodynamic Values Noted During the Anesthetic Management of a Patient With Osler–Weber–Rendu Syndrome and Severe Rheumatic Heart Disease

	ABP (mm Hg)	Pulse (beats/min)	CVP (mm Hg)	PAP (mm Hg)	PAOP (mm Hg)	CO (L/min)	FHR (beats/min)
Baseline	90/60	126	10	57/30	26	2.73	150
After diuresis and dobutamine	102/60	110	3	52/32	25	4.09	150
After epidural anesthesia	104/63	119	3	50/30	19	4.44	140
At delivery	100/50	110	2	40/20	20	4.41	—
Postpartum	112/57	109	2	46/22	18	5.1	—

ABP, arterial blood pressure; CVP, central venous pressure; PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output; and FHR, fetal heart rate.

syringe pump infusing 1% lidocaine at 12 mL/h over 20 min produced an L-1 level of anesthesia block. The infusion rate was subsequently increased to 20 mL/h, with a resultant T-10 sensory block in 30 min. This sensory level was maintained with a continuous infusion of 0.125% bupivacaine with 1:400,000 epinephrine at 10 mL/h. After the establishment of adequate analgesia, oxytocin was infused to induce labor, and an amniotomy was performed. During the active phase of labor, the patient required more intense analgesia. Accordingly, we infused a solution of 0.15% bupivacaine with 1:400,000 epinephrine and 2 μg fentanyl/mL at 12 mL/h for 7 h. The fetus tolerated the induction well with no cardiac decelerations by internal fetal heart rate monitoring. Nine hours after induction, a 1100-g male infant was delivered vaginally without forceps after 10 min of second-stage labor. His 1- and 5-min Apgar scores were 7 and 9, respectively, followed by an uneventful subsequent neonatal course.

Three hours after delivery, we changed the epidural infusion solution to 2% lidocaine with 1:200,000 epinephrine at 20 mL/h in preparation for a postpartum tubal ligation, performed uneventfully after a T-6 anesthesia level was achieved 60 min after the infusion was begun. The solution was then changed to 0.125% bupivacaine with the rate tapered over 6 h and then discontinued.

The epidural infusion was maintained for a total of 23 h. During this period, no significant variability in the hemodynamic values was noted (Table 1). Intravenous fluids were maintained at 75 mL/h. A transient reduction in arterial blood pressure with the patient's delivery efforts was treated with a 300-mL crystalloid bolus. Urine output averaged 1.5 $mL \cdot kg^{-1} \cdot h^{-1}$ throughout this period. Blood loss at delivery was considered average and caused no hemodynamic changes. Oxygen saturation by continuous pulse oximetry remained between 99% and 100%. Upon transfer to the medical intensive care unit 3 h after termination of the epidural infusion, no residual sensory or motor block was present. An arterial blood sample showed pH to be 7.44, $Paco_2$ 37 mm Hg, Pao_2 126 mm Hg, and oxygen saturation 97%. Postpartum hemodynamic values remained unchanged (Table 1). The patient recovered quickly with resolution of her congestive heart failure and was discharged 7 days after delivery on digoxin and captopril therapy.

Discussion

Osler–Weber–Rendu syndrome classically consists of a triad of telangiectasia, recurrent epistaxis, and a family history of the disorder (1), but more accurately is described as a disorder of telangiectatic bleeding, aneurysms, and AV fistulas of both the pulmonary and systemic circulatory systems. The underlying pathologic abnormality appears to be a combination of an insufficient smooth muscle contractile element, endothelial cell junction defects, and perivascular connective tissue weakness (1,4). In addition, increased tissue plasminogen activator in the abnormal endothelium may impair thrombus formation once bleeding begins. An association of disseminated intravascular coagulation, factor XI deficiency, and type II von Willebrand's syndrome with OWR disease has been reported (5).

Swinburne et al. have described OWR syndrome in a parturient with multiple pulmonary AV fistulas and worsening hypoxia secondary to an increased intrapulmonary shunt fraction (3). The authors suggested that the increase in blood volume associated with pregnancy may have distended the abnormal pulmonary AV fistulas. This distention may have increased the fistula blood flow relative to that of the normal pulmonary vasculature and thus increased the right-to-left shunt. In addition, new pulmonary AV connections may have developed during pregnancy (3), creating refractory hypoxemia with an increased risk of maternal and fetal mortality. Pulmonary fistulas can also increase the possibility of paradoxical emboli, whether from septic particles, amniotic fluid, air, or thrombi. Peripheral septic emboli may thus evade the filter of the pulmonary microvasculature and result in brain abscesses, which develop in approximately 6% of all patients with pulmonary AV fistulas (6). In our case, although the larger pulmonary AV fistulas were occluded by embolization, several smaller AV fistulas remained, in addition to presumed others too small for angiographic detection (1,6).

Congestive heart failure secondary to large AV shunts has been described in several patients as the initial manifestation of OWR syndrome (7). Indeed, two pregnant women with OWR syndrome developed large hepatic AV shunts with consequent congestive heart failure, hepatic dysfunction, and pulmonary hypertension (8). Although our patient showed no evidence of a large systemic AV fistula, worsening congestive heart failure could have been falsely attributed to rheumatic heart disease and pregnancy alone, and might have delayed the consideration of a possible occult systemic AV fistula.

Most authors consider epidural anesthesia to be the technique of choice for the management of labor and delivery in the pregnant patient with rheumatic heart disease (2,9,10), although intravenous narcotics, inhalational analgesia, intraspinal opiates, and various regional blocks have also been described. Cardiac output is increased approximately 30%–45% at term and an additional 20% during each uterine contraction secondary to both the cardiac response to pain and the shift of venous blood from the contracting uterus (2). Continuous lumbar epidural anesthesia provides analgesia, which attenuates the cardiac response to the pain of labor and delivery. We speculate that epidural anesthesia may alleviate the distention of preexisting pulmonary AV fistulas by reducing surges in cardiac output. Because of the possibility in OWR syndrome of paradoxical air embolization, air should not be injected into the epidural space. Instead, we suggest a loss-of-resistance test using saline to identify the epidural space.

Certain potential benefits and hazards exist in the use of epidural anesthesia in the parturient with rheumatic heart disease and severe mitral regurgitation. The sympathectomy induced by epidural anesthesia decreases left ventricular afterload and mitral regurgitation, thus enhancing forward flow from the ventricle. However, the concomitant increase in venous capacitance may require administration of intravenous fluids to keep the left ventricle "full" (9). Such volume loading before the epidural blockade may impose a large volume overload on the left ventricle and would not be desirable (11). Specific recommendations for the management of epidural anesthesia for this complex problem have not yet been suggested. The consensus in the literature is only that the epidural block for patients with severe mitral regurgitation be instituted "slowly and carefully" (9,10,12).

Although spontaneous epidural bleeding has not been described with OWR syndrome, the possibility of abnormal spinal and epidural vasculature in a syndrome characterized by multiple central and peripheral AV fistulas remains. In addition, the risk of an associated coagulation abnormality makes epidural catheter placement and possible resultant epidural hematoma an obvious concern for the anesthesiologist. A normal Ivy bleeding time, which may indicate the absence of pathology involving the vessel wall of a small area, gives no assurance of the normalcy of the epidural venous system. In our patient with severe cardiovascular disease caused by both rheumatic heart disease and OWR syndrome, the advantages of epidural anesthesia may have outweighed the possible risk of an epidural hematoma. Nevertheless, the placement of a needle into the subarachnoid or epidural space in a patient with multiple AV fistulas associated with OWR syndrome carries the attendant risk of an expanding epidural hematoma.

We initiated and maintained epidural anesthesia in a parturient with OWR syndrome and severe rheumatic heart disease using a standard syringe pump, a technique not described previously. The advantages of this approach were as follows:

(a) In a parturient with severe cardiac disease, but with adequate cardiac filling pressures, the slow onset of a sympathectomy provided by this technique allowed compensatory vasoconstriction and avoided the necessity of a standard fluid bolus to prevent hypotension. If a decrement in filling pressures had been observed, the intravenous administration of fluids could have been given in amounts adequate to maintain filling pressures.

(b) A machine performs the injection of local anesthetic, which may remove the possibility of excessive epidural injections with their undesired consequences and allow concentration on patient management.

In summary, recognition of a bleeding tendency, the risks of paradoxical emboli with pulmonary AV fistulas, and the possibility of high-output cardiac failure secondary to large AV fistulas constitute the major anesthetic considerations in the parturient with Osler–Weber–Rendu syndrome. The use of a syringe pump for the induction of epidural anesthesia is an approach that may provide remarkable cardiovascular stability in a patient with an unusual and severe combination of cardiovascular disorders.

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Letters to the Editor

Inexpensive Capnography During Monitored Anesthesia Care

Key Words: MONITORING, CAPNOGRAPHY. EQUIPMENT, CAPNOGRAPHY—nasal catheter.

To the Editor:

Since the arrival of capnographs on the anesthesia scene, we have sought ways to utilize these devices in evaluation of ventilatory adequacy in patients needing close monitoring during regional or local anesthesia (i.e., monitored anesthesia care, or MAC). The manufacturer of our capnographs supplies a nasal cannula-type device that, in our experience, functions poorly, is unnecessarily expensive (about $5 each), and is nonreusable.

We have found an inexpensive alternative that works much better. In Figure 1, arrow A identifies an ordinary nasal cannula (Airlife, Cat. No. 001312, American Pharmaseal Company) that has been cut off just proximal to the junction where the cannula divides into two cannulae. The extension tubing (not shown) is discarded. Arrow B identifies the capnograph tubing, which will be connected to the remaining portion of the nasal cannula. In Figures 2 and 3, the cut end of the nasal cannula (arrow A) and one end of the capnograph tubing (arrow B) are pictured in more detail. Figure 3 illustrates the precisely fitting connection between the cut nasal cannula and the capnograph connector.

First, the nasal cannula that is connected to the capnograph tubing is placed in the patient's nares in the usual fashion. Because most patients breathe through the nose, the shape of the CO_2 waveform rivals that obtained when connected to an endotracheal tube. If desired, a second nasal cannula may be placed through which O_2 is administered. When a concentration of O_2 greater than that obtained with the nasal cannula must be assured, the same device can be used simultaneously with a Venturi mask.

The above arrangement provides a method for qualitative monitoring of ventilation. The actual values obtained should be ignored, because this is not a quantitative monitor. As has been expressed by others, using a similar arrangement, we believe that changes in the capnograph waveform precede dangerous O_2 desaturations, as may occur during intravenous sedation (1). Although the apnea alarm may not be specific for apnea, as, for example, when the patient mouth-breathes, it is sensitive and obliges the anesthetist to evaluate the patient's ventilatory status.

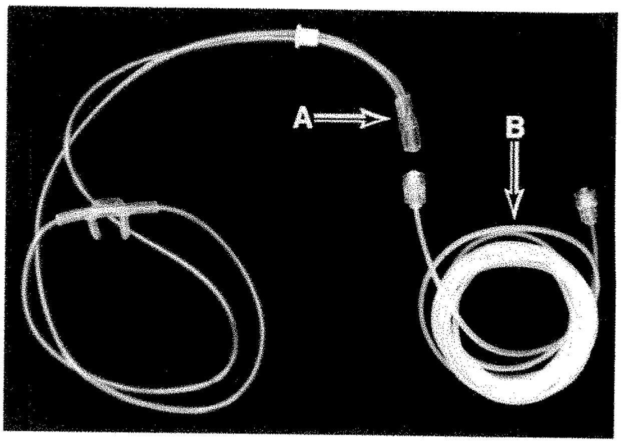

Figure 1. Cut nasal cannula (*A*); capnograph tubing (*B*).

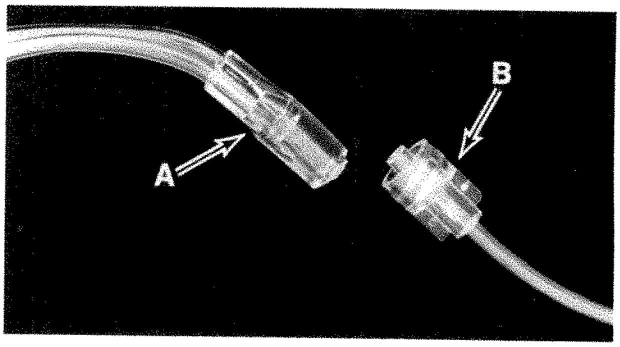

Figure 2. Cut end of nasal cannula (*A*); end of capnograph tubing (*B*).

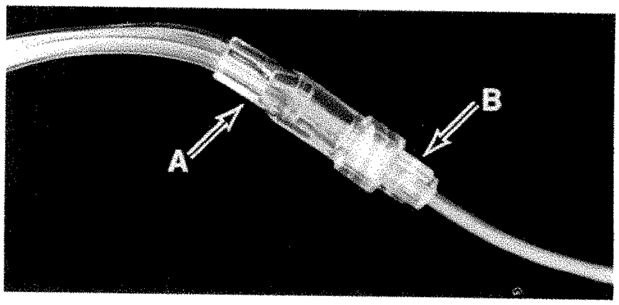

Figure 3. Nasal cannula (*A*) connected to capnograph tubing (*B*).

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So far we have received no complaints of discomfort from patients monitored in this fashion. The cost of the nasal cannula is only 25 cents, making it the least expensive device we have seen utilized for this purpose. The nasal cannula 1103 made by Hudson Oxygen Therapy Sales Company works equally well. It may be that nasal cannulae of all manufacturers work equally well because of standardization.

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Yes, Let's Standardize Our Nomenclature and Use "Arrhythmia"

Key Words: HEART, ARRHYTHMIAS—semantics. PUBLICATIONS, ANESTHETIC JARGON.

To the Editor:

I read with concerned interest Royster's letter to the editor regarding nomenclature for disturbances of the normal rhythmic beating of the heart (1). He has more than adequately reviewed the case for past use of either term—arrhythmia or dysrhythmia—to describe cardiac rhythm disturbances. However, I am in complete agreement with Dr. Royster that for the sake of clarity and consistency in communication between all workers in the field, regardless of discipline, we should adopt the word recommended by several official organizations/societies in the field of cardiology to describe any cardiac rhythm other than of sinus origin—namely, arrhythmia (2–4). Although I have used the words "arrhythmia" or "dysrhythmia" in several of my recent publications (5–7) as well as in two editions of a book on the subject (8), I believe we should all conform with the "consensus opinion" in future communications on the subject and stick to "arrhythmia."

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Subcutaneous Emphysema Associated With Laparoscopy

Key Words: COMPLICATIONS, EMPHYSEMA—subcutaneous. SURGERY, LAPAROSCOPY—emphysema.

To the Editor:

The laparoscopic CO_2 insufflator is commonly used today for many gynecologic procedures when abdominal distention is essential for good surgical exposure. Although many complications have been reported during laparoscopy, very little attention has been given to the insufflating machine itself. We report a case of subcutaneous emphysema that occurred because of a problem with the pressure-gauge indicator on the CO_2 insufflator.

A 29-yr-old woman, physical status ASA II, underwent laser laparoscopy for lysis of adhesions due to endometriosis. Routine monitoring was established with a blood pressure cuff, capnograph, pulse oximeter, electrocardiogram, precordial stethoscope, and neuromuscular blockade monitor. After midazolam premedication, general anesthesia was induced uneventfully with thiopental. Vecuronium was used to facilitate tracheal intubation. Anesthesia was maintained with an O_2/N_2O/narcotic relaxant technique using morphine sulfate. The patient was placed in a lithotomy with Trendelenburg position for the procedure. The Verres needle and trocar were inserted into the peritoneal cavity without difficulty. Pneumoperitoneum was created with a CO_2 automatic insufflator (Richard Wolf model 2043-50, Rosemont, Ill.).

About 2 h after the start of surgery, it became increasingly difficult to ventilate the patient. The peak airway pressures increased to 38 cm H_2O from 26 cm H_2O despite adequate depth of anesthesia and relaxation. The end-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) increased to 37 from 29 mm Hg, and the minute ventilation ($\dot{V}_E$) was adjusted from 7.4 to 11.8 L/min. Breath sounds were present and equal bilaterally, and there were no hemodynamic changes with a blood pressure of 120/85 mm Hg and a heart rate of 75 beats/min. The surgeons were advised that there was difficulty ventilating the patient. The procedure was completed, and soon afterward the pneumoperitoneum was released. When the drapes were removed, the patient was found to have subcutaneous emphysema of the anterior chest wall. Neuromuscular blockade was reversed with neostigmine and atropine. After the patient was awake and breathing spontaneously, she was extubated in the operating room. A chest x-ray in the recovery room showed subcutaneous emphysema but no pneumothorax.

When the CO_2 insufflator was examined by a clinical engineer, it became apparent that the intraabdominal pressure gauge was inaccurate. There was a nonlinear difference between the indicated setting and the actual pressure so that the pressure at the zero setting actually corresponded to approximately 18 mm Hg, at 20 to 28 mm Hg, and at 50 to 56 mm Hg. On manual control the insufflation should deliver 1 L/min of gas and stop spontaneously when the intraabdominal pressure reaches 50 mm Hg. Intraabdominal pressure is usually maintained between 15 and 25 mm Hg (1). The surgeons insufflate on manual control until they achieve adequate visualization. The insufflator is then placed on automatic control for the duration of the procedure. The rate of insufflation on automatic control is also at 1 L/min, but flow stops when intraabdominal pressure reaches the level achieved on manual control and resumes when the pressure decreases below this level. Because of the inaccuracy of the pressure gauge indication of the insufflator on this day, the pressure generated and delivered to our patient was approximately 10 mm Hg above the pressure on the pressure gauge of the insufflator.

The complication rate in laparoscopy is generally low. Subcutaneous emphysema is more commonly related to improper position of the needle (2,3). This case illustrates that the CO_2 insufflator machine may also be the source of a complication such as subcutaneous emphysema.

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Blood Transfusion, Anesthesia, and Host Defense

Key Words: IMMUNE RESPONSE, TRANSFUSIONS—inhalation anesthetics.

To the Editor:

We read with interest the article by Waymack et al. (1), which reported that both allogeneic blood transfusion (BT) and anesthesia increased susceptibility to intraperitoneal *Escherichia coli* infections in rats. The mean survival time as well as survival rate were significantly decreased in animals given a septic challenge 7 days after a BT, compared with control animals (survival time 4.41 ± 0.68 vs 6.55 ± 0.25 days; survival rate 21% vs 68%). In contrast, no differences were observed in these two parameters when the transfused rats were challenged with *E. coli* either on the day of transfusion or on days 3, 4, 5, and 6 after BT.

Also, these data are entirely different from those previously reported by these authors, which utilized the same strains of rats, the same BT protocol, and the same infectious agent (2). In the earlier report, rats were challenged with *E. coli*, either on the same day as the transfusion or 4 days after BT. Blood transfusion resulted in significantly decreased survival rates (20.8% and 33.3% when the organisms were given the same day or day 4 after BT, respectively) compared with control rats (50.0% and 63.0%). Similarly, discordant data are seen in the anesthetic groups.

It is disappointing that these authors make no attempt to explain the obvious discrepancies between their two reports. More important, why did these authors not even quote their earlier publication reporting the discrepant results (2)?

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In Response:

To answer Dr. Singal et al., the purpose of our initial study (1) was to determine whether there was any effect of anesthesia or BTs on survival in a peritonitis model. For that study, there were only two time sequences used, 0 and 4 days after transfusion or anesthesia, plus two doses of *Escherichia coli*, 1 × 10^7 cfu and 1 × 10^8 cfu. In our second study (2), having already established that there was an effect, a single dose of bacteria was used for all peritonitis protocols (1 × 10^7 cfu). However, two methods of administering the bacteria, peritoneally and intravenously, were studied. Further, the bacteria were given over a period of 1 wk after transfusion or anesthesia using six different time sequences to evaluate when the effect was maximal.

With regards to the effect of anesthesia on peritonitis, similar results were found at the two dates, which overlapped in both studies. With respect to BTs, there was no significant effect on survival time in either study at day 0. The decrease in survival rate at day 0 was present at only one concentration of bacteria in the initial study (1). This effect just barely achieved statistical significance. In the latter study, there was also a difference between transfusion and control groups at posttransfusion day 0; however, it failed to reach statistical significance. Because there were fewer animals used in the latter study, this may reflect a type II statistical error. In the initial study, the effect at day 4 was becoming more pronounced in the BT group. This was also true in the latter study, but, again, due to a decreased number of animals, this did not achieve statistical significance. In the latter study, the transfusion effect was maximal and achieved statistical significance when the animals were challenged 1 wk after transfusion. Therefore, we believe that, as is true in transplantation studies (3), the transfusion effect increases with time during the first 7 days after transfusion.

Using additional animals in our latter study may have avoided a type II statistical error, but the benefits achieved from the use of additional animals would have been of questionable value. The study had already succeeded in demonstrating that the transfusion effect increased with time during the first week after transfusion and that it did not affect resistance to an intravenous challenge of bacteria.

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Electrocardiographic Changes During Cesarean Section Under Regional Anesthesia

Key Words: ANESTHESIA, OBSTETRIC—ECG changes. HEART, ARRHYTHMIAS. ANESTHETIC TECHNIQUES, SPINAL, EPIDURAL.

To the Editor:

Palmer et al. (1) found electrocardiographic (ECG) changes suggestive of myocardial ischemia in 47% of 93 healthy term parturients undergoing elective cesarean section under spinal or epidural block preceded by the intravenous infusion of 2 L of electrolyte solution. As one of the possible causes of such myocardial ischemia, the authors referred to studies performed in nonpregnant volunteers that showed that sudden hypervolemia in the presence of sympathetic blockade increased myocardial work and myocardial oxygen demand (2). Using noninvasive cardiac-output monitoring in healthy gravid women, we found that a preload of 1600 mL of Ringer's solution and institution of epidural anesthesia for cesarean section can increase stroke volume by as much as 55%. An increase of such magnitude undoubtedly places a stress on the heart. Adding cardiac output or central venous pressure measurements to the seven-lead electrocardiogram in the above study may have shed more light on the etiology of the observed ECG changes.

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Inorganic Fluoride and Prolonged Anesthesia

Key Words: ANESTHETICS, VOLATILE—isoflurane. BIOTRANSFORMATION (DRUG), ISOFLURANE. IONS, FLUORIDE.

To the Editor:

We were interested to read the recent report by Truog and Rice (1) on the increase in serum fluoride concentrations after prolonged isoflurane anesthesia in a child. Their peak measured fluoride concentration was 36.8 μM/L, although we previously reported a higher reading of 93 μM/L with no deterioration of renal function (2). Isoflurane has many properties that make it an attractive sedative agent for critically ill patients, but data on the potential for fluoride toxicity in this situation are limited.

We have studied 14 patients in the intensive therapy unit who were expected to require ventilation for longer than 24 h. These were seven men and seven women with a mean age of 62 yr (range, 38–80) and normal renal function as assessed by plasma creatinine and urine osmolality. They were sedated with isoflurane at a mean inspired concentration of 0.29% (range, 0.1%–0.5%) for 34 (range, 10–74) h. This is equivalent to 8.6 (range, 1.22–21.6) MAC-h. The plasma concentrations of inorganic fluoride were measured before sedation, regularly during the period of sedation, and for a week afterwards, using an ion-selective electrode technique as previously described (3). The initial plasma concentration of fluoride was 3.18 (range, 0.68–6.53) μM/L and increased steadily during isoflurane sedation reaching 20.53 (range, 5.47–22.95) μM/L when the isoflurane was discontinued. The plasma fluoride concentration continued to increase, reaching a peak concentration of 22.06 (range, 8.3–34.53) μM/L 16 h after the withdrawal of the isoflurane sedation.

It is interesting that although these patients received considerably less isoflurane than the child reported by Truog and Rice, the plasma concentrations of fluoride were similar. This may be due to the fact that children metabolize isoflurane to a lesser degree or that isoflurane disposition is altered in critically ill patients. It is unlikely to reflect differences in analytical methods, although we measure plasma, not serum, fluoride concentrations.

It has been reported previously that serum fluoride concentrations continue to increase after isoflurane anesthesia (4) and it is interesting that in Truog and Rice's patient the fluoride levels decreased rapidly after discontinuing isoflurane. Although peak fluoride concentrations in our patients with normal renal function are lower than those reported to cause nephrotoxicity in fit patients (5), this may not be the case in patients with renal impairment. It is impossible to compare our series of critically ill adults with a child of 2 yr, but it emphasizes that more work is needed before isoflurane can be recommended to sedate either adults or children for prolonged periods in the intensive therapy unit.

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Is Cimetidine Indicated in the Treatment of Acute Anaphylactic Shock?

Key Words: HISTAMINE, CIMETIDINE. ALLERGY, ANAPHYLACTIC SHOCK.

To the Editor:

Although we read with interest the recent letter of De Soto and Turk describing the use of intravenous (IV) cimetidine for intraoperative anaphylactic shock (1), we wish to emphasize that the routine use of H_2 blocking agents for this disorder is controversial as well as theoretically detrimental. Indeed, one expert in this field has stated that "no clinical evidence indicates that administration of antihistamines is effective in treating anaphylaxis once mediators have been released" (2).

Several lines of evidence suggest that H_2 blocking agents are not useful in anaphylactic shock. First, as pointed out by De Soto and Turk (1), H_2 blockade appears beneficial only for urticarial manifestations of anaphylaxis. Because large studies of intraoperative anaphylaxis clearly document the rarity of urticarial signs and symptoms (8%–14%) and the overwhelming predominance of cardiovascular collapse (≥90%) (3,4), the anesthesiologist has little to gain by administering an H_2 blocking drug in this setting. Furthermore, in these series bronchospasm occurred in 23%–37% of patients and could be exacerbated due to unopposed H_1 activity on bronchial smooth muscle. The risk of further hypotension, which has been reported with rapid IV administration of cimetidine (but not ranitidine) (5,6) must be considered. Information extrapolated from data on gastric acid suppression in normal volunteers suggests that significant levels of H_2 blockade occur 30–40 min after a loading dose of IV cimetidine (7). Although the vascular system may well respond more rapidly, the pharmacokinetics of these agents make them unlikely to help the clinician faced with life-threatening anaphylactic shock.

The H_2-receptor activity has many favorable effects in anaphylactic shock, including increased inotropy, increased chronotropy, and coronary vasodilation (8). H_2-receptor stimulation also exerts a negative feedback to diminish further release of vasoactive mediators from basophils and mast cells (9,10). Studies evaluating pretreatment regimens for patients at high risk for IV contrast media reactions document that the addition of cimetidine to a three-drug protocol (diphenhydramine, prednisone, ephedrine) leads to a higher occurrence of repeat reactions compared with the three-drug combination alone or a similar two-drug regimen (diphenhydramine and prednisone) (11). Although all three pretreatment regimens significantly reduce the incidence of recurrent life-threatening reactions, the data certainly suggest that H_2 blockade was not beneficial.

The cornerstones of treatment of anaphylactic shock continue to be oxygen, IV fluids, and epinephrine. Initial fluid requirements may be substantial, with one large study suggesting that 50% of circulating plasma volume may be lost within the first 15 min (3). Preexisting volume deficits from overnight fasting before surgery would only magnify this hypovolemia. In addition, patients in shock have greatly lengthened circulation times. Peripheral IV to central circulation time during cardiopulmonary resuscitation (where central mean arterial pressure is typically ≤40 mm Hg) has been shown to take up to 2 min (12,13) and results in lower peak drug levels compared with central drug administration (12). We hypothesize that the response attributed to cimetidine in the patient reported by De Soto and Turk may reflect the cumulative effect of prior epinephrine administration in the face of a prolonged circulation time. In 276 cases of intraoperative anaphylactic shock (3), a strong association existed between prolonged resuscitation, subsequent mortality, and the late use of epinephrine. Only six patients failed to respond to adequate fluid therapy and epinephrine. Three of these six nonresponders subsequently responded to an infusion of norepinephrine (3). Aggressive volume resuscitation coupled with frequent, escalating titration of epinephrine should clearly be the focus of treatment for this disorder. Whether H_2 blocking agents offer any further benefit is uncertain.

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Treatment of a Delayed Reaction to Droperidol With Diphenhydramine

Key Words: ANESTHETICS, INTRAVENOUS—droperidol.

To the Editor:

The use of droperidol antiemetic prophylaxis has become controversial because of equivocal results pertaining to its efficacy and because of its side effects. The article by Melnick et al. (1) described gynecologic patients complaining of being nervous the day after their ambulatory surgery. These patients received droperidol as an antiemetic without effect on the incidence of postoperative nausea.

A similar occurrence involved a 16-yr-old girl with Ellis von Crevald syndrome who had an orthopedic appliance removed from her right leg. The patient's multiple orthopedic procedures in the past had been complicated by postoperative nausea. After an inhalation induction with halothane, nitrous oxide, and oxygen, 0.625 mg droperidol and 50 μg fentanyl were administered. The mask anesthetic was uneventful. The patient was discharged home after a few hours, satisfied with her anesthetic, without postoperative nausea.

After an uneventful evening, the patient awoke the next morning disoriented as to time. She complained of being dissociated from her environment and described herself as an "observer" unable to interact with what was going on around her. The feeling made her very restless and uncomfortable. There were no other systemic complaints, and, because the patient was a considerable distance from the hospital, I recommended 50 mg diphenhydramine (Benadryl). Her uncomfortable sensations subsided within an hour after taking the diphenhydramine.

This case report reveals three important questions about the routine use of droperidol as an antiemetic. First, even a small, seemingly innocuous dose of droperidol (0.625 mg) may cause an extrapyramidal reaction. Second, the onset of these reactions can be delayed beyond the 14 h described in Melnick's article. In this case onset occurred almost 24 h later. Third, drug-induced extrapyramidal reactions respond readily to low-dose anticholinergics (2). The central antimuscarinic effects of diphenhydramine blunt the excitatory action of the cholinergic system on the nigrostriatal pathways. Diphenhydramine not only halted this disconcerting reaction in this patient, its sedating action relieved her.

This infrequently reported reaction is extremely distressing to those who experience it. This reaction may be unrecognized because its onset is delayed, and because patients are not asked if they are experiencing this during our postoperative assessment. Diphenhydramine's anticholinergic action appears useful in the therapy of this untoward effect of droperidol. Like any medication, the risks and benefits of the use of droperidol as an antiemetic must be weighed before casually giving this drug.

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Intrathecal Combination of Bupivacaine-Fentanyl-Morphine

Key Words: ANESTHETIC TECHNIQUES, SPINAL—bupivacaine-fentanyl-morphine combination. PAIN, POSTOPERATIVE.

To the Editor:

At our hospital, we have been combining 0.5 mL of fentanyl (25 mg) and 0.5 mL of spinal bupivacaine (3.75 mg) with 0.5–0.6 mL (1 mg/mL) of preservative-free morphine for intrathecal administration, in order to control postoperative pain after donor nephrectomy. This mixture is given after surgery and shortly before awakening. The analgesia produced is prompt in onset and profound in quality. Patients are comfortable upon arrival to the recovery room, and the analgesia lasts for about 18 h. Thereafter, a smooth transition is made to patient-controlled analgesia. In a group of 10 patients given this combination, supplemental postoperative analgesia was needed in only two of them, and only for a total of four doses (using either 10 mg of intravenous meperidine or 1 mg of intravenous morphine during the first 18 h after surgery). Both of these patients were extremely satisfied with their analgesia.

Neuroaxial narcotics are known to block the release of substance P (1). Intraspinal morphine has a slow onset (more than 30 min) because it is hydrophilic. Fentanyl hastens onset of analgesia because it is lipophilic (2). Bupivacaine, working at the axonal level of the A delta and C fibers, is known to potentiate spinal morphine antinociception (3). The ultimate goal of this combination is to have an intrathecal mixture that has a rapid onset, thereby *preventing* pain transmission through the dorsal horn. The prevention of nociception is key to the efficacy of neuroaxial narcotics (4).

Currently, there is no single drug available that provides both rapid onset and prolonged analgesia. Combination drug therapy might represent a rational alternative. Whether this combination truly proves to be superior to intrathecal morphine alone or morphine plus fentanyl still awaits further study. It is our clinical impression that it does.

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Side Effects After Droperidol

Key Words: ANESTHETICS, INTRAVENOUS—droperidol.

To the Editor:

In a recent article, Melnick et al. describe how droperidol, in doses of 1.25 mg IV, did not decrease postoperative nausea or vomiting when compared with control, and how droperidol in this dose did contribute to anxiety or restlessness after discharge (1). It is not surprising that they were not able to show a significant reduction in nausea and vomiting with droperidol. First, a power analysis would have revealed that their sample size was inadequate to show that a 50% reduction was significant, given that only 14% of the control patients had nausea and 6% had vomiting. Second, the dose of droperidol that they used was too large: in two studies, droperidol in a dose of 0.25 mg was more effective in reducing postoperative vomiting than 0.5 mg droperidol (mean weight 60 kg) (2) and was more effective in reducing nausea than 1.25 mg droperidol (mean weight 62 kg) (3). Presumably, if a lower dose of the drug and a larger sample size were used, the ability of the drug to affect nausea, vomiting, and postoperative anxiety or restlessness would have been assessable.

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Book Reviews

Brain Storming: The Science and Politics of Opiate Research

Solomon H. Snyder. Cambridge, Mass.: Harvard University Press, 1989, 208 pp, $22.50.

Who discovered the opiate receptors? Was it Solomon Snyder, through his studies of stereospecific binding of radioactively labeled opiates? Others working in the receptor field, i.e., Candice Pert, Eric Simon, Avram Goldstein, and Lars Terenius, might not agree. If you can toss that thorny question aside and not let the business of how scientific credit is established bother you, and if you can overlook the unsophisticated view of the role of politics in medical research, the book is an excellent introduction to molecular neuroscience. For those who never get close to the true masters of laboratory research, Snyder presents an exciting story of his quest for the opiate receptors and his involvement in the isolation of the enkephalins.

Occasionally throughout his story, he drops his own pearls for successful grant-writing, dictating a first draft, and making scientific discoveries. He is convinced that the creative aspect of scientific discovery is best communicated through the mentor-student relationship, and the best way to predict who will make a worthy discovery is to examine who trained whom. The book is very much a tribute to his own great teacher, the Nobel laureate, Julius Axelrod.

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Regional Anesthesia

An Illustrated Procedural Guide. 1st ed.

Michael F. Mulroy. Boston: Little Brown & Co., 1989, 289 pp, $42.50.

Regional Anesthesia is a refreshing new manual on practical aspects of regional blocks whose strength lies in the fact that it achieves a simple literary style without compromising on the essentials. The author deserves credit for making this difficult subject interesting and engaging. The manual is well designed; it is written by a clinician who is obviously very familiar with the material that is presented. The preface states that the manual is meant to be used as a practical guide in the places where procedures are performed, and the manual lives up to this claim with clear and concise descriptions of a variety of commonly performed blocks, which are appropriately buttressed by visually appealing illustrations. Each chapter contains a reference list that provides a guide for the reader who desires further information.

The first five chapters act as an introduction to the rest of the book, which consists of 14 chapters describing different blocks followed by three other chapters, of a general nature, that address obstetric anesthesia, pediatric anesthesia, and pain management. The first two chapters that deal with the pharmacology of local anesthetics are particularly good, providing important introductory information and setting the stage for the material that is to follow.

The book has a few minor shortcomings that need mention. Some areas of regional anesthesia require more detailed accounts. Management of complications such as excessively high spinal anesthesia in obstetric patients, bupivacaine toxicity, postspinal headache, and aspiration pneumonitis are not only management dilemmas, but also potential medicolegal issues and deserve more emphasis. Interpleural blocks and spinal and epidural opioids are relatively new techniques that require a more complete discussion. Additionally, to aid the novice in the choice of a specific block it would have been helpful to include a list of possible indications to assist in selecting the most appropriate block. Finally, the chapter on pediatric regional anesthesia, written by Lynn Broadman, MD, who is an associate professor of anesthesiology at the National Children's Hospital Medical Center in Washington, D.C., is especially informative.

In conclusion, at $42.50 this illustrated manual on regional anesthesia is a welcome addition to every anesthesiologist's library and should be carried to the operating room for quick reference. It fills a gap that currently exists, and this reviewer has no hesitation in recommending it to his residents. Other books on this subject are expensive and voluminous, making this manual attractive as a "how to" text.

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Introduction to Critical Care

J. M. Civetta, R. W. Taylor, and R. R. Kirby.
Philadelphia: J.B. Lippincott, 1989, 311 pp, $29.95.

In 1988 Civetta, Taylor, and Kirby provided the medical community with a comprehensive textbook entitled *Critical Care*. Whereas this first textbook dealt extensively with medical diagnosis and treatment of disease, their recent publication, *Introduction to Critical Care*, deals with the equally important nonmedical concerns. It examines the economic, ethical, legal, and political issues encountered when caring for patients. The book accurately captures the spirit of an intensive care unit (ICU), and is probably most useful to the more senior members of the ICU team, who must consider these issues along with the patient's medical care.

The authors have divided the book into two parts. The first part deals with the basic concepts inherent in the intensive care environment and provides a clear introduction to the issues. The topics included are setting objectives for care, clinical decision making, and ethical, legal, and economic considerations for an ICU. The balanced and constructive nature of the book is well illustrated in the second chapter, where "vantage points" are presented to classify the different types of ICU patients. By relating these patients to previous studies that examine severity of illness indexes to overall mortality, individual classifications provide a perspective for clinical decision making. The other chapter of particular importance is the concise summary of the legal decisions in critical care. The discussion progresses from the criteria for brain death to the current legal decisions regarding the "quality of life" issue. The authors also show how these decisions have evolved over time and probably will continue to change.

The second part of the book deals with the "people" aspects of intensive care. The first chapter, written by nurses, precisely captures the spirit of the unit and provides a basis of understanding for the "smart resident" to adjust his/her ego when working in this environment. The underlying theme of this section deals with the personalities and various expectations of different members of the team. The descriptions are accurate and balanced. It essentially states and supports the notion that the intensive care physician needs not only sound medical knowledge but the ability to deal and care for each member of the ICU team.

One of the last chapters addresses details of medical care that are "poorly appreciated and undervalued" by many individuals. This chapter on preventive care points out very important details in a patient's care and relates back to an earlier chapter on "iatrogenesis." The book provides history and perspective for all individuals working in the unique environment of an intensive care unit.

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Atlas of Cardiothoracic Surgery

L. H. Edmunds, Jr., W. I. Norwood, and D. W. Low.
Philadelphia: Lea & Febiger, 1990, 287 pp, $25.00.

Although this atlas is intended for cardiothoracic surgeons and trainees, those involved in the practice of cardiothoracic anesthesia will find this book helpful and unique. The outstanding illustrations and short paragraphs of text describe the anatomy and techniques of cardiac and thoracic surgery. It does not, nor is it intended to, discuss physiology, indications for surgery, or pre- and postoperative care.

The authors, who are from the University of Pennsylvania and Children's Hospital of Philadelphia, include common procedures designated as cardiothoracic operations by the American Board of Thoracic Surgery and the Residency Review Committee. A wide range of surgery, including some variations that have proven effective and safe in the authors' hands, is presented. The atlas is divided into sections that cover incisions used in cardiothoracic surgery, aortic surgery, acquired cardiac disease, congenital cardiothoracic and vascular procedures, pulmonary and mediastinal operations, and esophageal disease. The brief, concise, step-by-step descriptions of each operation are written by experienced surgeons and teachers.

Special mention must be made of the superb illustrations, which set the book apart from any other text. The black and white drawings are clear, large, and keep the reader well oriented. Dr. Low has been very successful in creating artwork with a three-dimensional quality. It is not diagrammatic, but rather is quite realistic. Perhaps because the illustrator is both an artist and surgeon, nothing gets lost in the translation from operating room to atlas. The drawings are sequentially numbered, each with a corresponding paragraph on the facing page to help the reader follow the steps of the surgical procedures. Some illustrations do appear in *Cardiovascular Anesthesia and Postoperative Care* (Chicago: Year Book, 1982) edited by Tarhan. However, an anesthesia text cannot be expected to include figures that are as complete in scope and of as uniform quality as are found in the atlas.

Just as when an excellent heart surgeon makes a difficult procedure appear very simple, this atlas presents the steps in cardiovascular surgery in an easily understandable and organized manner. The foolish novice may almost believe, armed with this book and some self-instruction, that he or she is ready to perform chest surgery. Practitioners and students of anesthesia for cardiothoracic surgery are encouraged to review this atlas. After doing so, many will find it a necessity for their department libraries.

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Neuromonitoring in Surgery

J. E. Desmedt, ed. New York: Elsevier, 1989, 373 pp, $155.00.

The tremendous increase in intraoperative evoked potential monitoring requires that anesthesiologists be familiar with the techniques, influencing factors, and outcome of such monitoring. A knowledgeable and cooperative anesthesiologist greatly enhances the efficiency of intraoperative monitoring. The perfect text about intraoperative monitoring should provide basic understanding as well as sufficient examples to allow the physician to interpret and react to the varied monitoring circumstances encountered in the operating room.

This book is well organized, with each chapter broken down into 6 to 10 areas with easy access to specific areas. The editor was effective in molding this multiauthored text so that the format of the chapters were similar. Each author delineated the scope of his presentation early in the chapter, introduced appropriate physiologic concepts, and discussed technical aspects in an orderly manner.

Monitoring modalities covered in depth are motor evoked potentials, visual evoked potentials, brainstem auditory evoked responses, and somatosensory evoked potentials. The topics of electromyography and compound muscle action potential are introduced in a format appropriate for the beginner. In addition, there is a nice chapter about monitoring of cranial and peripheral nerves in which specific suggestions are presented for monitoring cranial nerves and specific peripheral nerves.

A chapter re monitoring neuromuscular transmission during anesthesia is also included. Although initially the presence of this chapter seemed odd, the editor's logic eventually became clear. The editor obviously assumed that nonanesthesiologists would have the greater part of the responsibility for neurologic monitoring and should at least understand how to evaluate neuromuscular blockade. The degree of neuromuscular blockade is important in assessing motor evoked potential, which is currently assessed using electromyography.

This book is filled with examples of changes in evoked potentials. The figures are generally reproductions of original data. As such they are not glamorous, but repeated exposure to them prepares the reader to evaluate evoked potential in a format produced by evoked potential machines. The examples are fine in detail, but the text fails to indicate the sense of urgency required to make a timely diagnosis of change in evoked potentials. Individual chapters contain clear examples of artifact that might be encountered during intraoperative monitoring. Considering the importance of rapidly determining if evoked potential changes are due to artifact, perhaps a chapter devoted to sources and presentation of artifact would have been a welcome addition to the text.

An anomaly in the book's organization is a chapter titled "Surgical Monitoring With Evoked Potentials: The Mayo Clinic Experience." The reason for this addition is unclear. It essentially discusses topics covered in many other chapters. This chapter also contains detailed menus that add little to the educational impact of the chapter.

This book will make a useful addition to the library of the anesthesiologist who has some understanding of intraoperative evoked potential monitoring. Although a valuable resource book, it does not provide a sufficiently broad prospective to allow the completely naive anesthesiologist to function independently in intraoperative monitoring. However, the wealth of information is useful to the neophyte as well as to the experienced individual.

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Essentials of Anesthesiology. 2nd ed.

David C. Chung and Arthur M. Lam. Philadelphia: W.B. Saunders, 1990, 320 pp, $21.50.

To the uninitiated, the practice of anesthesiology is mysterious. Misconceptions abound among both lay and medical personnel. The new edition of *Essentials of Anesthesiology* attempts to demystify and explain the basic concepts of this branch of medicine. Designed specifically as a primer text for clinical clerks on anesthesia rotations, the book is both appropriately comprehensive and concise. The 24 chapters deal with a broad spectrum of anesthesia-related topics, from molecular mechanisms of anesthetics to the implications of the acquired immune deficiency syndrome in anesthesia practice. The text is extremely readable and has few typographical errors. Clinical clerks, beginning anesthesia residents, and residents from other specialties should find it invaluable as a means of rapid orientation to a new specialty. The length should allow one to read it completely during the first few days of a rotation, the size for it to be carried in a coat pocket, and the comprehensive index to find and review selected topics rapidly.

As is the case with any introductory text, the authors were challenged by the difficult task of deciding what information to include and what to omit. In general they have succeeded admirably. Although most of the topics are covered only briefly, a wealth of information is provided. The beginning student of anesthesia will repeatedly refer to the sections on muscle relaxants and monitoring of neuromuscular function. The section on preoperative assessment will provide the neophyte anesthetist with guidance during the first few preoperative visits. In similar fashion, the section on postoperative care of the patient during recovery outlines the common postanesthetic considerations and complications in an easily understood, systematic fashion.

The authors have also included a section on anesthetic mishaps, quality assurance, and risk management, as well as an appendix containing the ASA standards for basic intraoperative monitoring. These topics must be thoroughly understood by all practitioners of our specialty. The coverage provided is succinct, well-written, and easy to understand. One might argue, however, that because of their primary importance, these topics could have been placed at the front of the book to provide a context in which to consider the clinical didactic material.

There are, however, several areas that could be managed in a more practical fashion. Chapter 22, "Cardiopulmonary Resuscitation," is a topic with which most medical school curricula deal extensively through formal courses in Basic and Advanced Cardiac Life Support. Chapter 23, "Resuscitation of the Newborn," is a specialized area, perhaps unlikely to be of value to the beginning or temporary practitioner. Chapter 21, "Blood Transfusion in Surgical Patients," contains a considerable quantity of advanced or controversial concepts. Chapters 7, 8, and 9 deal with the "hardware" of anesthesia practice and should be expanded because a thorough understanding of the equipment is mandatory for the safe administration of anesthesia. Such information, in a readily digestible form, is priceless for a novice practitioner. Although standard textbooks deal with these topics extensively, the student will not have ready access to those sources. Chapter 9, "Mechanical Ventilation," addresses a topic that most clinical clerks find intimidating. An expanded treatment of this subject matter would be most useful for students and junior house staff alike.

In summary, this book is a concise, well-written primer for students beginning to study the art and science of anesthesiology. The authors have not taken a "cookbook" approach; rather, they have produced a small, readable text that can also serve as a primary reference. Constraints of size impose necessary limitations on the scope and coverage of topics. Despite these restrictions, the authors have succeeded in producing a useful and informative text.

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Anesthesia in Emergency Medicine

Glenn S. Vanstrum, ed. Boston: Little Brown & Co., 1989, 445 pp, $45.00.

The role of anesthesiologists is expanding in the continuum of patient care. Their intraoperative roles and contributions are well defined, and postoperative involvement in pain management and critical care continues to grow. However, few anesthesiologists venture retrograde in this continuum to the preoperative emergency phase or, for that matter, the prehospital phase of care, unless specifically requested. Although there are anesthesia manuals that address issues for emergency surgery (*Practical Anesthesia for Surgical Emergencies* by Peter W. Jackson and *Manual of Anesthesia for Emergency Surgery* by Judith H. Donegan), currently there is no text available that discusses the role of the anesthesiologist in the emergency room (ER) environment.

The stated goal of *Anesthesia in Emergency Medicine* is to seek common ground and to bridge the knowledge gap between the specialities of anesthesiology and emergency medicine. The forward by Peter Safar, MD, adds credibility to this endeavor by defining "reanimatology" (the science of resuscitation and life support) as the scientific foundation of commonality between the two specialities. As a self-proclaimed "reanimatologist," this reviewer wholeheartedly endorses Vanstrum's intentions and applauds his initiative. However, the big question remains: "Is this book of any value to the clinical anesthesiologist, and, more important, should one spend one's hard-earned dollars to add it to one's library?"

Anesthesia in Emergency Medicine consists of 15 chapters written by nine authors that span a wide array of topics of interest to the anesthesiologist venturing into the ER. The intended audience is not just anesthesiologists, however, but also ER physicians, who rarely have a good working understanding of what the anesthesiologist has to offer in the ER environment. Herein lies the book's main strength or weakness, depending on one's point of view.

The chapter on pharmacology is excellent. It includes a nice summary of pertinent pharmacokinetics and pharmacodynamics and discusses the anesthetic agents, both inhalation and intravenous, that may be used in the ER. The chapter is well referenced, with tables and charts that are clear, concise, and informative. It is an excellent source of information for the ER physician, but its contents are common knowledge to most clinical anesthesiologists. In a similar way, well-written chapters on pulmonary and cardiac considerations will benefit the ER physician to a greater extent than most anesthesiologists.

Conversely, the chapter on trauma management is as good as any currently found in a major anesthesiology text. The section on cervical spine protection is well referenced and recommends the technique that most trauma anesthesiologists recognize as the safest for endotracheal intubation. The segment on fluid resuscitation is concise and well written, with most recommendations adequately referenced.

A separate chapter on airway management concludes with 14 case presentations, encompassing difficult airway management problems encountered in the ER and suggesting various management options and recommendations. Anesthesiologists who find themselves in the ER infrequently will find this of particular value.

The chapter on legal issues will be of interest to most anesthesiologists: the concepts of informed consent, good-Samaritan laws, and the rights of Jehovah's Witnesses regarding blood transfusion are well covered. The chapter on infectious disease considerations contains nothing new for the anesthesiologist or the ER physician with a section on AIDS that is glaringly incomplete. The chapter on regional anesthesia is targeted primarily for the ER physician and discusses those blocks commonly performed in the ER—with the exception of the Bier block, which is one of the most commonly used blocks in the ER.

Other chapters include pain management, pediatric, obstetrical, and gynecologic perspectives, and gastrointestinal and renal considerations, as well as a section on head injuries. Most anesthesiologists will find these chapters to be superficial reviews of topics discussed in depth in other anesthesiology texts.

The book concludes with a chapter on disaster medicine, which confronts the reader with the realities of our medical system's inability to handle any but the smallest disasters effectively. The effects of the detonation of a relatively small nuclear warhead over Hiroshima on the medical system's ability to meet the needs of victims is vividly detailed in text and photographs.

There are topics of interest to the anesthesiologist involved in ER care that were not discussed. The role of the anesthesiologist in prehospital care and transportation of critically ill patients, either by land vehicle or aircraft, was omitted. A discussion on the role of Nitronox for analgesia in the prehospital phase and a recommendation regarding its use were both absent. Airway management in the patient with drug overdose (an area that this reviewer finds controversial and at times troublesome) is mentioned only in passing. The role of the anesthesiologist in the initial assessment and care of patients sustaining burns or inhalational injuries was also not discussed.

In summary, *Anesthesia in Emergency Medicine* is generally a well-written, well-referenced endeavor intended to enlighten both anesthesiologists and ER physicians about common issues. There are a few mistakes in the text, but they do not detract from its usefulness. Emergency room physicians will benefit most from this addition to the medical literature. Resident anesthesiologists and clinicians who only rarely visit the ER will benefit from this book, which is reasonably priced at $45.00 and should find its way into many anesthesiology and ER libraries.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Bankert M. *Watchful Care: A History of America's Nurse Anesthetists.* New York: Continuum, 1990, 234 pp, $24.95.

Bonke B, Fitch W, Millar K, eds. *Memory and Awareness in Anesthesia.* Amsterdam, The Netherlands: Swets and Zeitlinger, 1990, 394 pp.

Guzman MF, Hedley-Brown A, Been M, Cook S, Wren C, Richens D. *Manual of Cardiorespiratory Care.* Butterworths, 1989, 314 pp, $29.95.

Lee KJ. *Textbook of Otolaryngology and Head and Neck Surgery.* New York: Elsevier Science Publishing Co., 1990, 951 pp, $125.00.

Mangano DT, ed. *Preoperative Cardiac Assessment.* Philadelphia: J.B. Lippincott, 1990, 192 pp, $38.00.

Martyn JA, ed. *Acute Management of the Burned Patient.* Philadelphia: W.B. Saunders, 1990, 341 pp, $50.00.

Mason RA. *Anaesthesia Databook, a Clinical Practice Compendium.* New York: Churchill Livingstone, 1990, 529 pp, $50.00.

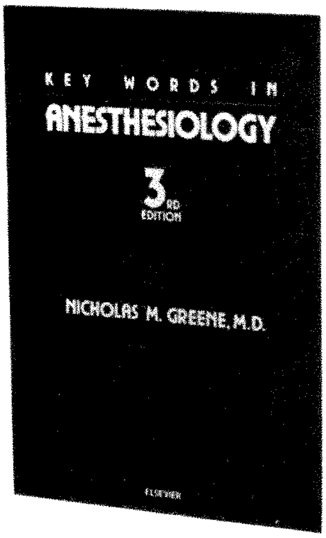
McLeskey CH, ed. *Perioperative Geriatrics.* Problems in Anesthesia, Volume 3, No. 4. Philadelphia: J.B. Lippincott, 1989, $25.00 single issue, $60.00 annual subscription of four issues.

Porter SS, ed. *Neuroanesthesia.* Problems in Anesthesia, Volume 4, No. 1. Philadelphia: J.B. Lippincott, 1990, 236 pp, $30.00 single issue, $65.00 annual subscription of four issues.

Reisner LS, ed. *Obstetric Anesthesia.* Anesthesia Clinics of North America, Volume 8, No. 1. Philadelphia: W.B. Saunders, 1989, 221 pp, $27.00 single issue, $86.00 annual subscription.

Stanley TH, Sperry RJ, eds. *Anesthesiology and the Heart.* Boston: Kluwer Academic Publishers, 1990, 346 pp, $115.00.

Weinstein PR, Faden AI. *Protection of the Brain from Ischemia.* Current Neurosurgical Practice Series. Baltimore: Williams & Wilkins, 1990, 307 pp, $85.00.



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A Guide for Authors

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The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766-71 and *Lancet* 1982;284:1766-70.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, by parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

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☐ Original articles describe in 3000 words or less clinical or laboratory investigations.

☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.

☐ Technical communications are papers that deal with instrumentation and analytic techniques.

☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.

☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.

☐ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in.) using double spacing throughout.

☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

☐ Submit three copies of manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter, and pemissions to reproduce previously published materials or to use illustrations that may identify subjects.

☐ Authors should keep copies of everything submitted.

Title Page

☐ The title page should contain the title of the article, which should be concise but informative;

☐ A short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified;

☐ First name, middle initial, and last name of each author, with highest academic degree(s); each listed author must a) have participated in the work to the extent that he or she could publicly defend its contents; b) have read the manuscript prior to its being submitted for publication; and c) be prepared to sign a statement to the effect that he or she has read the manuscript and agrees with its publication.

☐ Name of department(s) and institution(s) to which the work should be attributed;

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☐ Name and address of author responsible for correspondence about the manuscript.

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Abstract and Key Words

☐ The second page should carry an abstract of not more than 150 words. (Abstracts are not needed for Clinical Reports.)

☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.

☐ Define all abbreviations except those approved by the International System of Units.

☐ Key (indexing) terms: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article and that may be published with the abstract.

Text

☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion.

☐ Case reports, reviews, and editorials do not require the above sections.

☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are

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not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.

☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.

☐ *Units of measurement:* Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in **SI units** with, if desired, present conventional metric units in parentheses.

References

All references must be available to all readers. Cite only references to books and articles or abstracts published in peer reviewed *Index Medicus* journals. Abstracts appearing only in programs of meetings are not acceptable, nor are abstracts more than five years old.

☐ Number references consecutively in the order in which they are first mentioned in the text, except in review articles when references may be arranged alphabetically.

☐ Identify references in text, tables, and legends by arabic numbers (in parentheses, on line)

☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus.*

☐ The titles of journals must be abbreviated according to the style used in *Index Medicus.*

☐ References must be verified by the author(s) against the original documents.

☐ Examples of correct forms of references are given below:

Journals:

1. *Standard journal articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.) You CH, Lee KY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980; 79:311–4
2. *Personal author(s) books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
   Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

Tables

☐ Type each table double spaced on a separate sheet. Do not submit tables as photographs.

☐ Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading.

☐ Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use lower-case italicized letters in alphabetical order.

☐ Do not use internal horizontal or vertical rules.

☐ Cite each table in the text in consecutive order.

☐ If data are used from another published or unpublished source, obtain permission and acknowledge fully.

Illustrations

☐ Submit three complete sets of figures. Figures should be in black and white only and professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Note: Art work of published articles will not be returned.

☐ Instead of original drawings, roentgenograms, or other material send sharp, unmounted, glossy black-and-white photographic prints, usually 127 by 173 mm but no larger than 203 by 254 mm.

☐ Each figure must have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them by using paper clips. Do not bend figures.

☐ Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.

☐ Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.

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☐ Type legends for illustrations double spaced starting on a separate page, with arabic numerals corresponding to the illustrations.

☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

Abbreviations

☐ The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement. Avoid abbreviations in the title.

☐ Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

Exclusive Publication Statement

☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a covering letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.

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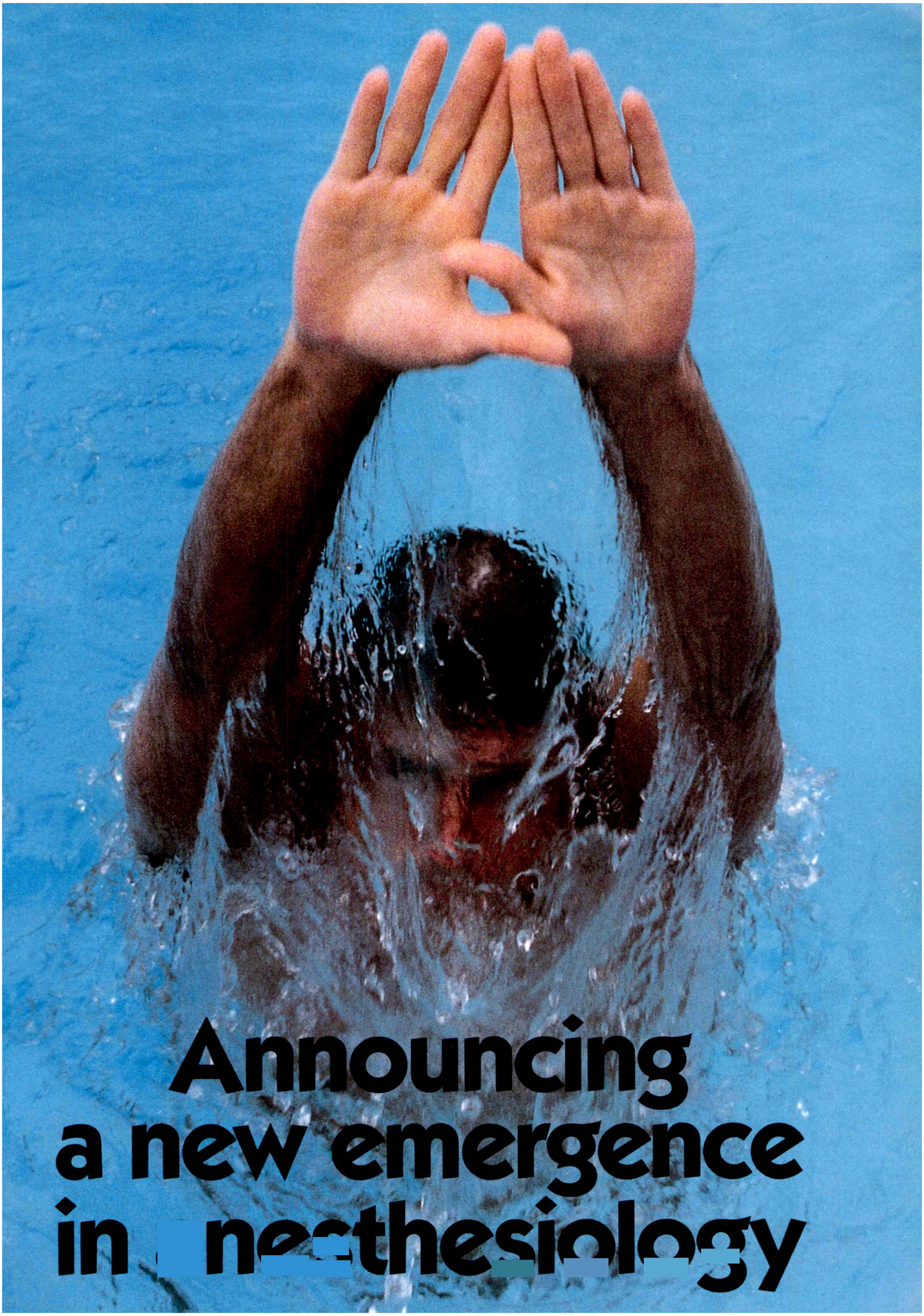
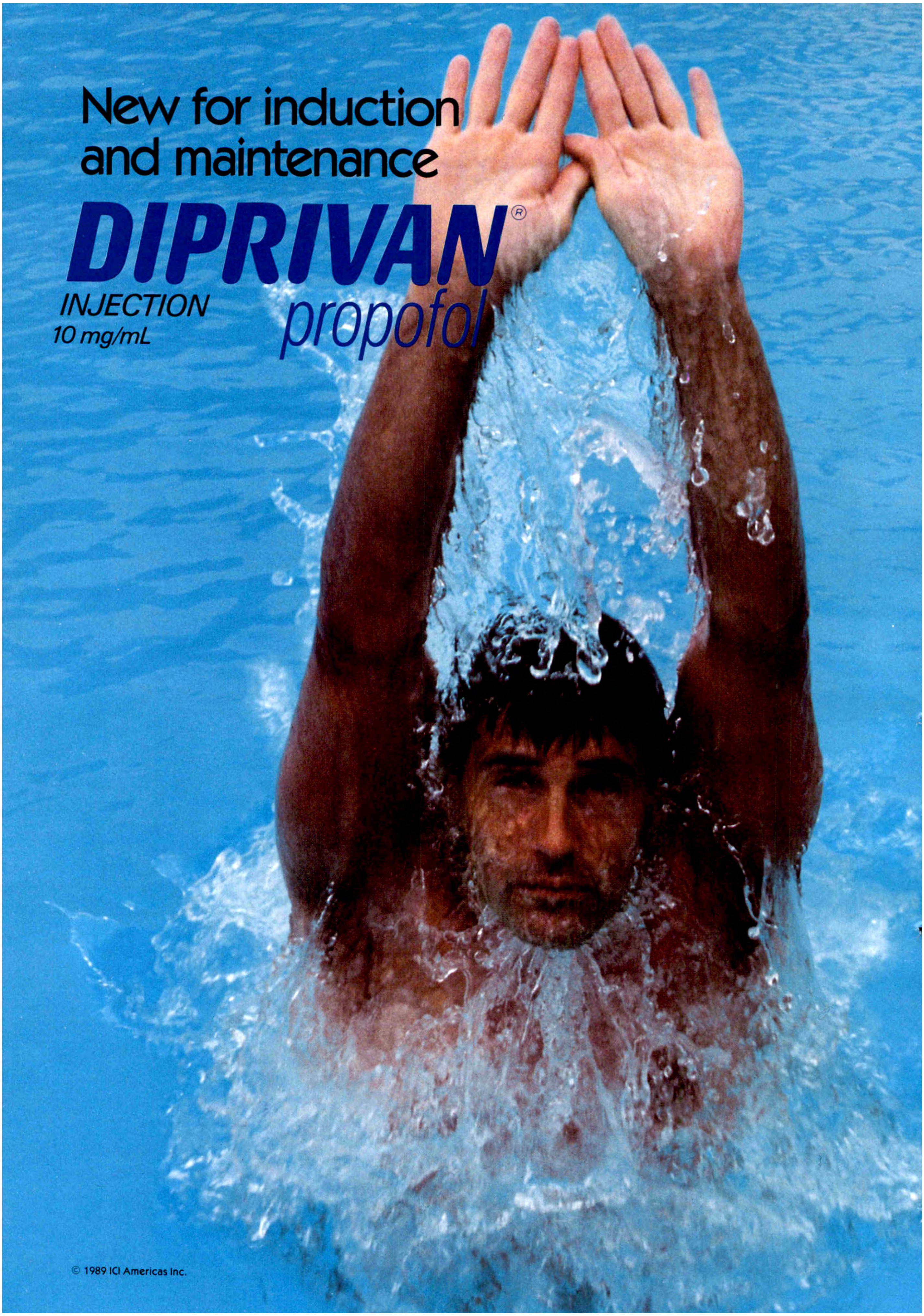

Announcing
a new emergence
in anesthesiology



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Superior recovery

Improved speed and quality of recovery compared with thiopental/isoflurane:

- more rapid time to extubation[5]
- more rapid and clearheaded awakening[6-8]
- lower incidence of nausea and vomiting[2,7]
- patients able to tolerate fluids faster[2,4]

Earlier discharge from PARR*

- more efficient utilization of OR/PARR facilities[9]
- increased nursing efficiency[9]
- rapid return to routine self-care activities

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

*An adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia.

DIPRIVAN®
INJECTION
propofol

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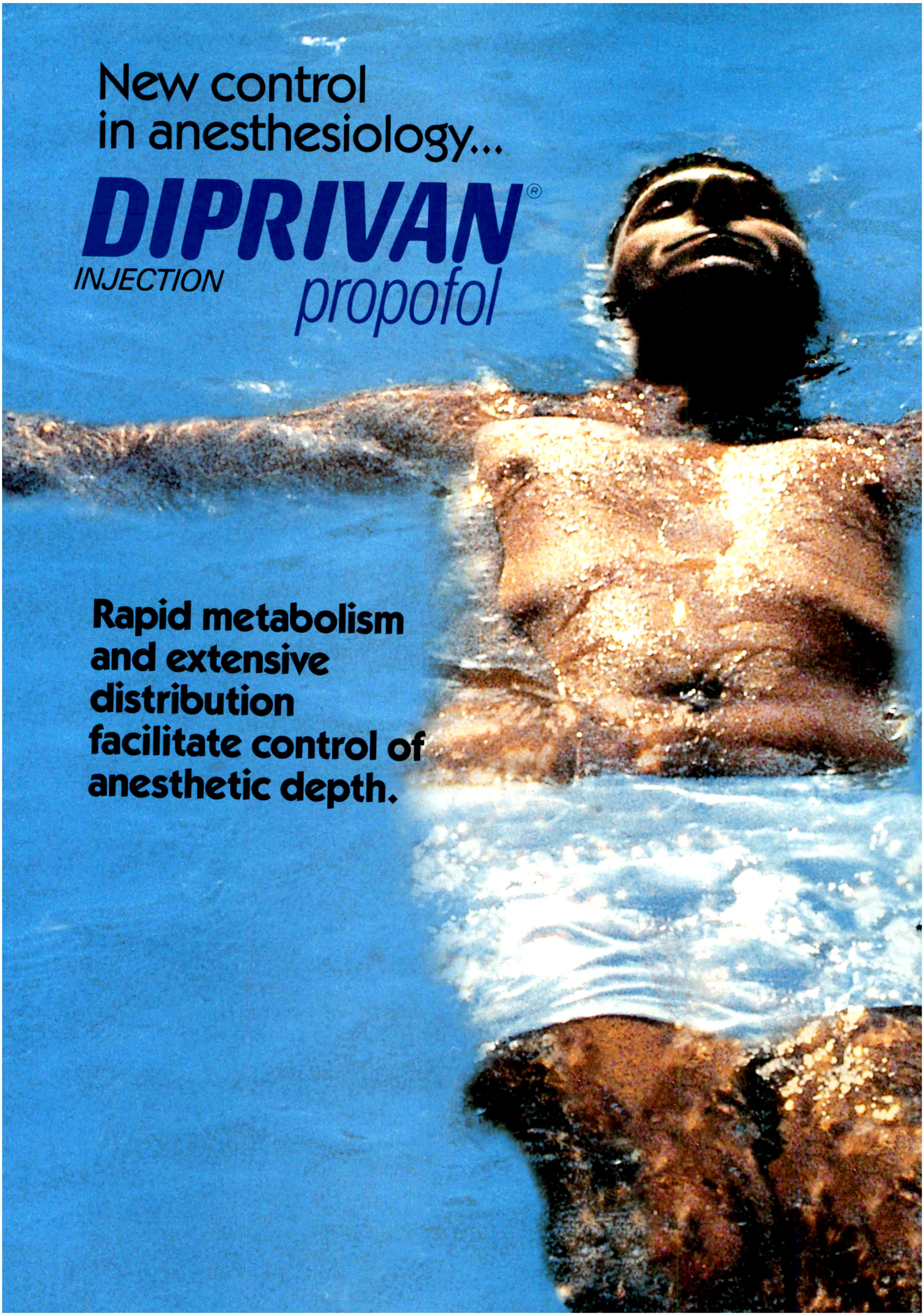
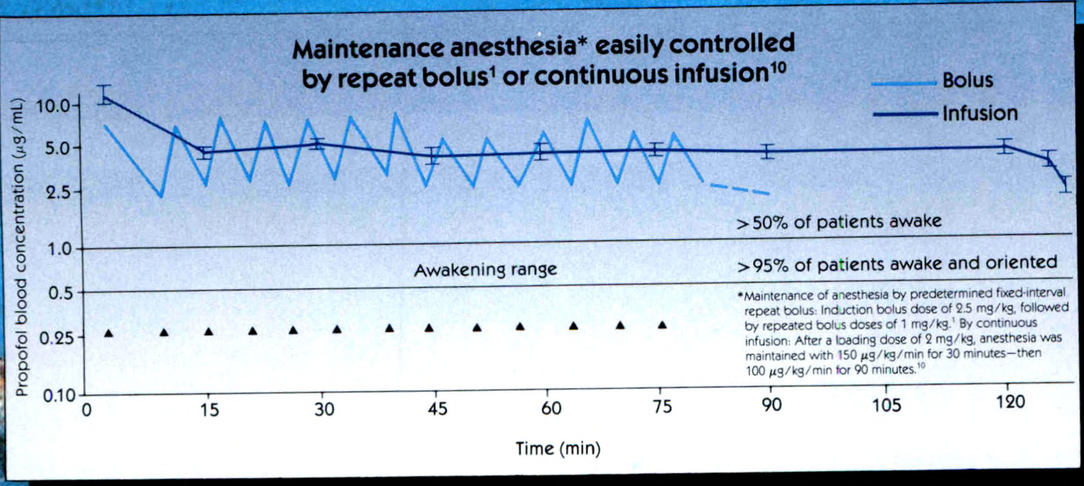

New control
in anesthesiology...
DIPRIVAN®
INJECTION
propofol
Rapid metabolism
and extensive
distribution
facilitate control of
anesthetic depth.

Maintenance of anesthesia: easily controlled


Maintenance anesthesia* easily controlled by repeat bolus[1] or continuous infusion[10]

*Maintenance of anesthesia by predetermined fixed-interval repeat bolus: Induction bolus dose of 2.5 mg/kg, followed by repeated bolus doses of 1 mg/kg.[1] By continuous infusion: After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[10]

—adapted from Cockshott, p 48,[1] White, p 9,[8] and Herregods et al, p 364[10]

No reported awareness during maintenance with DIPRIVAN

Overall quality of maintenance anesthesia superior to thiopental/isoflurane.[11]

Assessment of maintenance*[11]

	Excellent	Good	Poor
DIPRIVAN (n = 50)	**58%**	**30%**	**12%**
Thiopental + isoflurane (n = 50)	36%	32%	32%

*Statistically significant differences between all treatment groups ($P < 0.05$, Mantel-Haenszel Test)—as measured by the percent variation from baseline in hemodynamic parameters.

—adapted from Weingarten and Youngberg, data on file[11]

When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

DIPRIVAN®
INJECTION
propofol

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New assurance in anesthesiology...

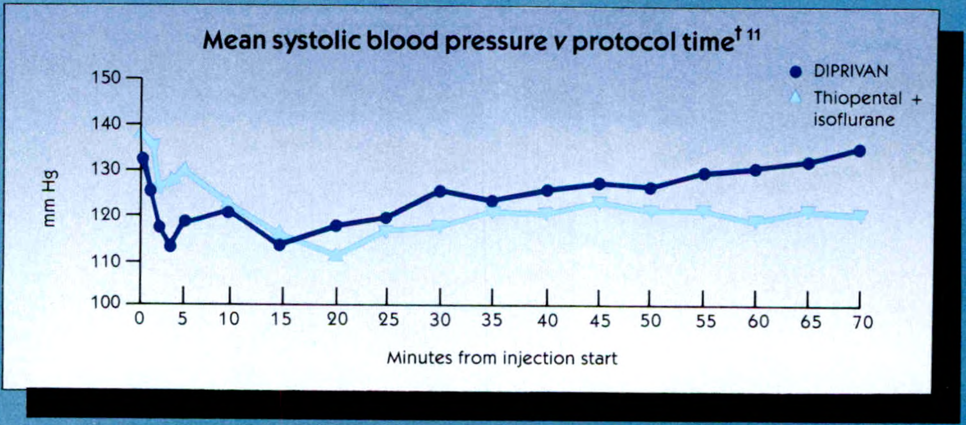
DIPRIVAN®

INJECTION propofol

Worldwide experience in over 7,000,000 patients

Hemodynamic and respiratory effects are dose-dependent

- Hemodynamic effects during induction were generally more pronounced than with traditional IV induction agents.
- Blood pressure predictably decreased on induction (sometimes >30%) but was within acceptable ranges for healthy individuals.*



Mean systolic blood pressure *v* protocol time†[11]

—adapted from Weingarten and Youngberg, data on file[11]

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†Induction bolus dose: Patients received either DIPRIVAN 2.5 mg/kg or thiopental 5.0 mg/kg. DIPRIVAN patients were then maintained with repeated injections of 25% of the original induction dose supplemented with 60% to 70% nitrous oxide in oxygen. Thiopental/isoflurane patients were maintained with 0.2% to 2.0% isoflurane supplemented with 60% to 70% nitrous oxide in oxygen.[11]

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

The first of a new class of IV anesthetic agents for induction and maintenance

DIPRIVAN, an alkylphenol, provides:

Rapid, predictable onset

- smooth induction with minimal excitation (one arm-brain circulation)

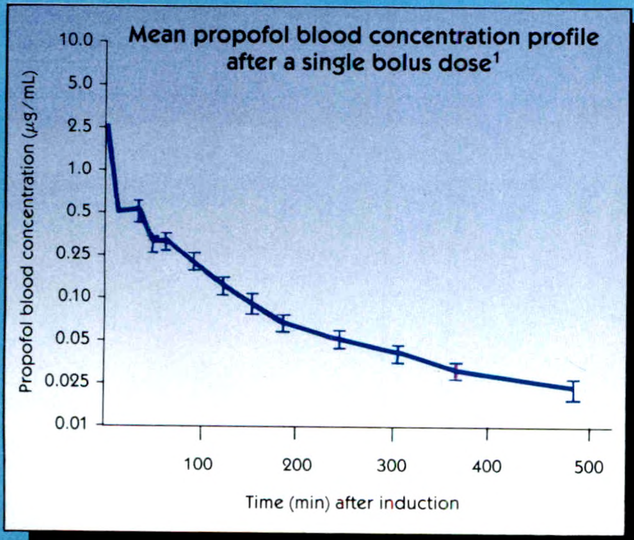
Rapid metabolism and extensive distribution*

- total body clearance exceeds estimates of hepatic blood flow[1]
- no active metabolites

Rapid, clearheaded awakening

- majority of patients are generally awake, responsive, and oriented within 8 minutes
- low incidence of nausea and vomiting[2]

*As with most anesthetic agents, the clearance rate of DIPRIVAN decreases in elderly patients.



Mean propofol blood concentration profile after a single bolus dose[1]

—adapted from Cockshott, p 46[1]

DIPRIVAN clearance
5-10 times faster **than barbiturates**

	Clearance rate (L/min)[†]
DIPRIVAN	1.6–3.4
thiopental[3]	.11–.30
methohexital[3]	.70–.84

[†] Calculations of clearance rates based on 70-kg patient.
—adapted from Way and Trevor, p 803[3]

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New awakening in anesthesiology...

DIPRIVAN®

INJECTION propofol

Alert emergence

Significantly faster recovery profile

Awakening was faster with DIPRIVAN than with thiopental/isoflurane...and DIPRIVAN patients were considered suitable for discharge significantly ($P < 0.05$) sooner.[4]

Mean postanesthesia recovery times (min)[4]

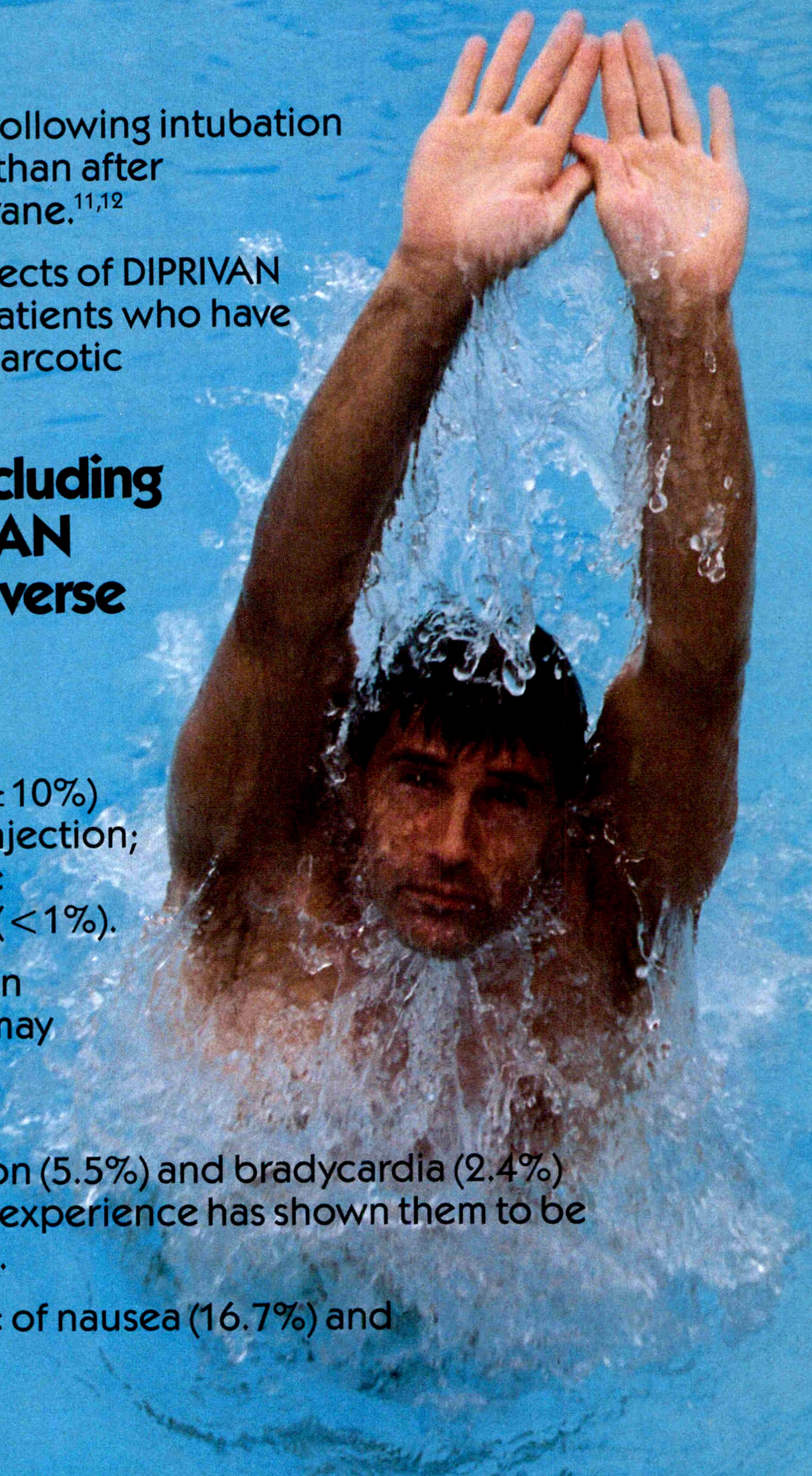
	DIPRIVAN	Thiopental/isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Eyes open spontaneously	4.0*	6.3
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
Able to stand unassisted	68	87
Able to walk unassisted	70	96
Able to void	102*	173
"Ready" for home	138*	206

*Statistically significant ($P < 0.05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

With less of the nausea and vomiting associated with other anesthetic agents—up to 24 hours postop

- Increase in heart rate following intubation was less pronounced than after thiopental with isoflurane.[11,12]
- The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.*

In clinical trials including over 1500 DIPRIVAN patients, most adverse events were mild and transient



- Transient local pain ($\geq$10%) may occur during IV injection; venous sequelae have rarely been reported (<1%).
- Apnea often occurs on induction (43%) and may persist for more than 60 seconds.
- Significant hypotension (5.5%) and bradycardia (2.4%) have been reported†; experience has shown them to be clinically manageable.
- Low overall incidence of nausea (16.7%) and vomiting (9.1%).

*Induction dose requirements may be reduced.

†Sufficient to require intervention.

DIPRIVAN®
INJECTION
propofol

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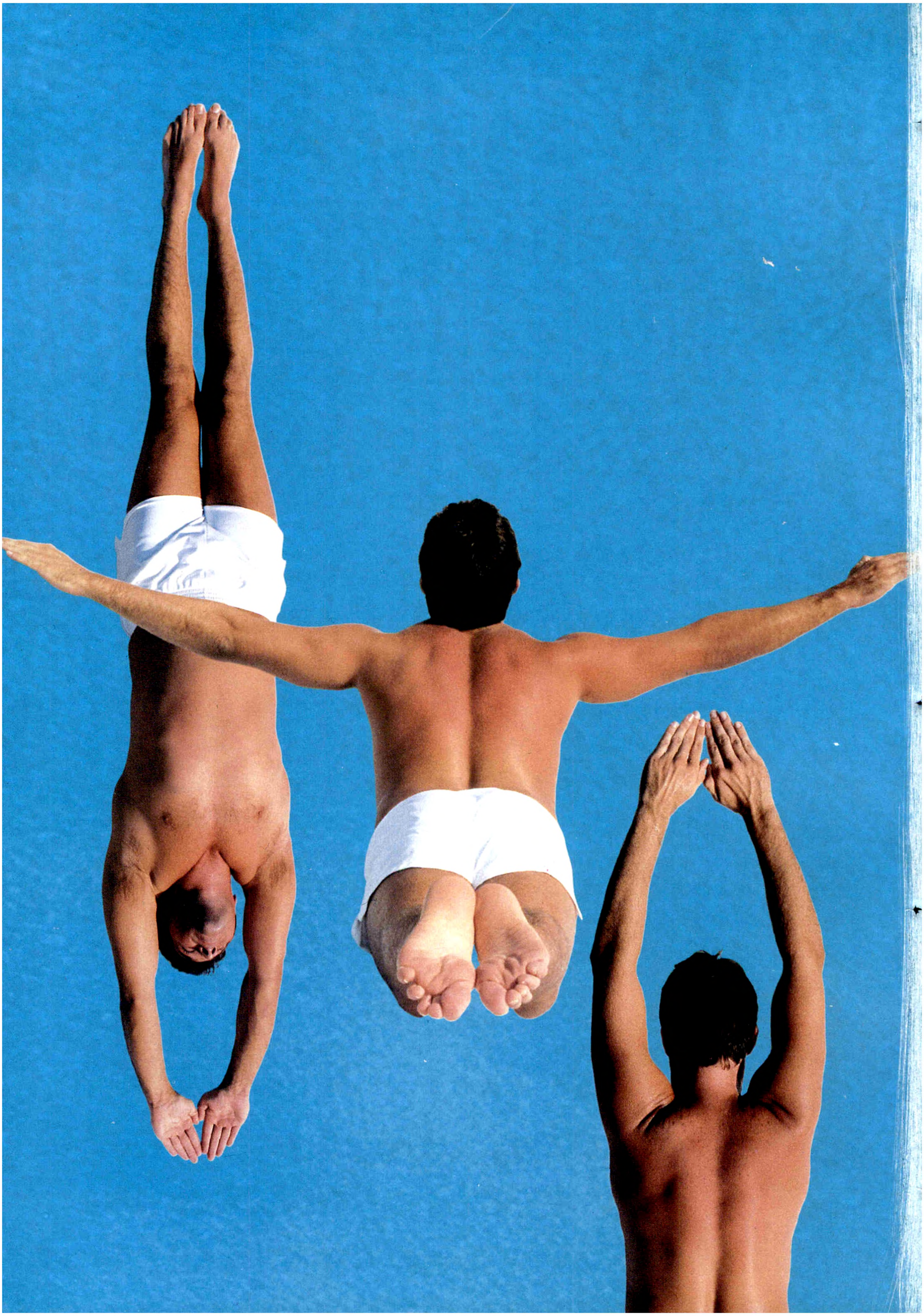


New versatility
in anesthesiology...

DIPRIVAN®

INJECTION propofol

For a wide variety of procedures... outpatient and inpatient

- Gynecologic
- Orthopedic
- ENT
- Urologic
- Dermatologic
- General surgery
- Ophthalmic
- Diagnostic

DIPRIVAN should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN should be used with caution in elderly, debilitated, and/or hypovolemic patients, and those rated ASA Class III or IV.

DIPRIVAN is not recommended at this time for use in pediatric patients, nursing mothers, patients with increased intracranial pressure or impaired cerebral circulation, and in obstetrics, including cesarean section deliveries.

- DIPRIVAN can be combined with other commonly used agents in anesthesia.
- Also eliminates concerns about operating room/ recovery room pollution associated with volatile agents.

Please see last pages of this advertisement for full prescribing information.

For induction
and maintenance...

DIPRIVAN®

INJECTION
10 mg/mL
propofol

The new IV anesthetic agent with a unique pharmacokinetic profile

- for rapid, predictable onset of anesthesia
- for smooth induction with minimal excitation
- for easily controlled maintenance of anesthesia
- for rapid, clearheaded awakening—with a low incidence of nausea and vomiting

Extensive worldwide experience

in a wide variety of surgical procedures—
outpatient and inpatient

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

REFERENCES: **1.** Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50. **2.** Korttila K, Faure E, Apfelbaum J, Östman P, Roizen M. Less nausea and vomiting after propofol than after enflurane or isoflurane anesthesia. *Anesthesiology.* 1988;69(3A):A578. Abstract. **3.** Way WL, Trevor AJ. Pharmacology of intravenous nonnarcotic anesthetics. In: Miller RD, ed. *Anesthesia.* 2nd ed. New York, NY: Churchill Livingstone; 1986:803. **4.** Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. **5.** Cork RC, Scipione P, Vonesh MJ, Magarelli JL, Pittman RG. Propofol infusion vs. thiopental/isoflurane for outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A563. Abstract. **6.** Vinik HR. Exponential infusion of Diprivan (propofol): a randomized comparison with methohexital and thiopental/isoflurane for induction and maintenance of anesthesia. *Semin Anesth.* 1988;7(suppl 1):94-98. **7.** Weingarten M. Diprivan (propofol) for induction and maintenance of general anesthesia: experience from two clinical studies. *Semin Anesth.* 1988;7(suppl 1):85-90. **8.** White PF. Propofol: pharmacokinetics and pharmacodynamics. *Semin Anesth.* 1988;7(suppl 1):4-20. **9.** Marais ML, Maher MW, Wetchler BV, Korttila K, Apfelbaum JL. Reduced demands on recovery room resources with propofol (Diprivan) compared to thiopental-isoflurane. *Anesthesiol Rev.* 1989;16(1):29-40. **10.** Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. **11.** Weingarten M, Youngberg JA. A multicenter, comparative study of Diprivan for the induction and maintenance of anesthesia by repeat bolus administration versus thiopental sodium for induction followed by inhalation anesthesia for maintenance. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. **12.** Gold MI, Sacks DJ, Grosnoff DB, Herrington CA. Comparison of propofol with thiopental and isoflurane for induction and maintenance of general anesthesia. *J Clin Anesth.* 1989;1:272-276.

DIPRIVAN®

INJECTION
10 mg/mL

propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

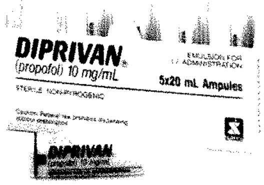
WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.



Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents.

The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset)
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

HOW SUPPLIED: DIPRIVAN Injection (NDC 0038-0290) is available in ready-to-use 20-mL ampules containing 10 mg/mL of propofol.

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

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354B/G

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359B/G

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406E/G

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411E/H

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419E/J

ANESTHESIOLOGY RESIDENCY POSITIONS
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424F/L

ANESTHESIOLOGIST
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428F/I

OHIO
BC/BE, to join group of 11 anesthesiologists and CRNAs at 500-bed, university-affiliated hospital on Ohio's north coast. All types of surgeries except organ transplantation. Send CV and two references to Associates

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in Anesthesia, 11311 Shaker Boulevard, Cleveland, OH 44104.

431FG

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434F/I

OHIO STATE UNIVERSITY, COLUMBUS
The Department of Anesthesiology is recruiting board certified/eligible anesthesiologists for clinical/tenure track appointments at the Instructor, Assistant, Associate, and Professor levels. Responsibilities will include resident and medical student teaching, independent research, and patient care. We are an Affirmative Action/Equal Opportunity Employer. Please send CV to J.S. McDonald, MD, Professor and Chairman, Ohio State University Hospitals, Department of Anesthesiology, 410 West 10th Avenue, Columbus, OH 43210.

435F/H

TENNESSEE
Anesthesiologist: Periodically full-time positions become available at the level of Instructor/Assistant Professor. Applicants must be board certified or in the board process and be interested in resident teaching and clinical research. Tennessee license required. If you would be interested in having your name on file, please reply with curriculum vitae to John T. Chesney, MD, Interim Chairman, Department of Anesthesiology, University of Tennessee Medical Center at Knoxville, 1924 Alcoa Highway, Knoxville, TN 37920. UTMC is an Affirmative Action/Title IX/Section 504 Employer.

436F/L

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437FG

NEW YORK
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393F/H

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425FG

ANESTHESIOLOGIST
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440G

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441G

ANESTHESIOLOGIST
BE/BC needed to join three-man group in Midwest. Send inquiries, CV, and references to Box 442 G/I.

442G/I

MINNESOTA
Four-member anesthesiologist group, part of an 80-member multispecialty clinic, is seeking a board certified/eligible anesthesiologist to replace a retiring member. Anesthesia team care provided at a secondary referral hospital (no OH) and freestanding surgery center. Candidate with interest in organizing chronic pain therapy would be given particular consideration. West Central Minnesota location affords recreational and outdoor opportunities. Send CV and three current references to Box 443 GIK.

443GIK

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444G

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445G/I

OHIO

Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity/affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, Ph.D., Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

446G/L

ANESTHESIOLOGIST

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447G/I

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448G

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Nemours Children's Clinic is seeking a Chief of Pediatric Anesthesiology to head its Department of Pediatric Anesthesiology. Candidate must be board certified in Anesthesiology and preferably in Pediatrics as well. He/she must have a pediatric anesthesiology fellowship or the equivalent in experience and be highly qualified in clinical and teaching skills. This position carries an academic appointment at the University of Florida College of Medicine. We seek a candidate with excellent academic credentials to direct a multifaceted academic department in an expanding medical center with a strong affiliation with the University of Florida. Interested applicants should send curriculum vitae to Dr. H. Warner Webb, Chairman of Anesthesiology Search Committee, Associate Medical Director and Surgeon-in-Chief, Nemours Children's Clinic, P.O. Box 5720, Jacksonville, FL 32247. Academic status is offered by the University of Florida, an Equal Opportunity/Affirmative Action Employer with whom Nemours is affiliated.

449G

OREGON

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450G/I

SOUTHERN CALIFORNIA

Olive View Medical Center, a UCLA-affiliated Los Angeles County hospital, is seeking academically qualified anesthesiologists. Board certified or in process required. Training in OB, pediatrics, or neuro desired. No OH or trauma. Please send CV with three references to Anesthesia Search, Department of Anesthesiology, Olive View Medical Center, 14445 Olive View Drive, Sylmar, CA 91342. Equal Opportunity Employer.

451G

ANESTHESIA GROUP

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453G

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454G/I

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455G/I

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344C/H

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383C/L

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384C/H

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335A/L

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432F/K

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380GH

OHIO STATE UNIVERSITY, COLUMBUS

The Department of Anesthesiology is recruiting board certified/eligible anesthesiologists as a Director of Ambulatory Surgery with specific training and/or experience in adult outpatient surgery. Responsibilities include management of 40–50 patients per day case load as well as resident teaching, research, and patient care. We are an Affirmative Action/Equal Opportunity Employer. Please send CV to Chairman, Faculty Search Committee Ohio State University Hospitals, Department of Anesthesiology, 410 West 10th Avenue, Columbus, Ohio 43210.

457G/J

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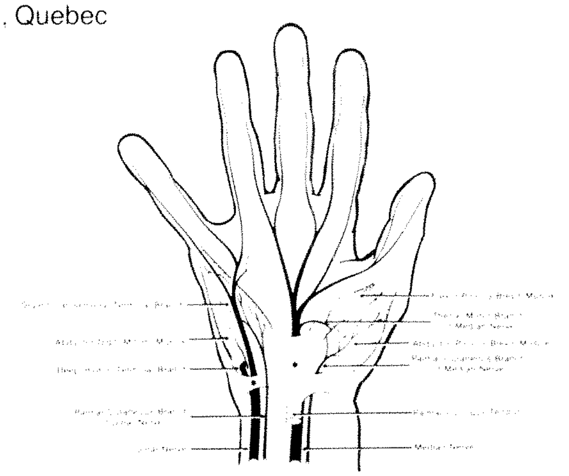

FIGURE 12.1 Palmar view of the right wrist and hand, showing the course and branching of the median and ulnar nerves. These nerves first divide into the common digital nerves, which then divide further to become individual proper palmar digital nerves. The transverse carpal ligament and its extension, which forms the roof of Guyon's canal, are marked with asterisks.

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In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours Single use only. Discard unused portion.

REV. 3/

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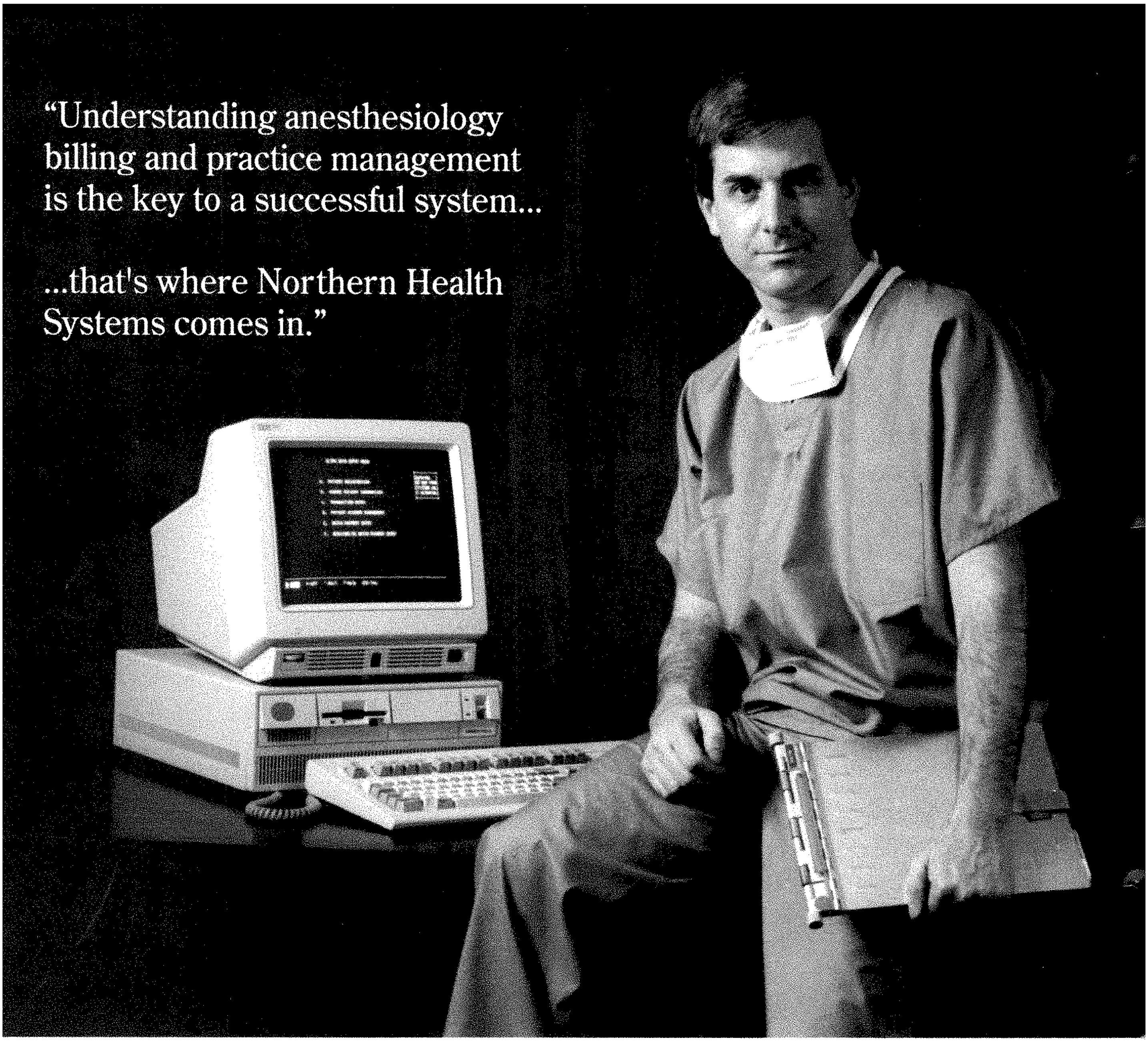
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References: 1. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982;56:112-118. 2. Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. 3. Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. 4. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. 5. Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.

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INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.
CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.
Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.
Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.
ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:
Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement
DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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Anesthesia
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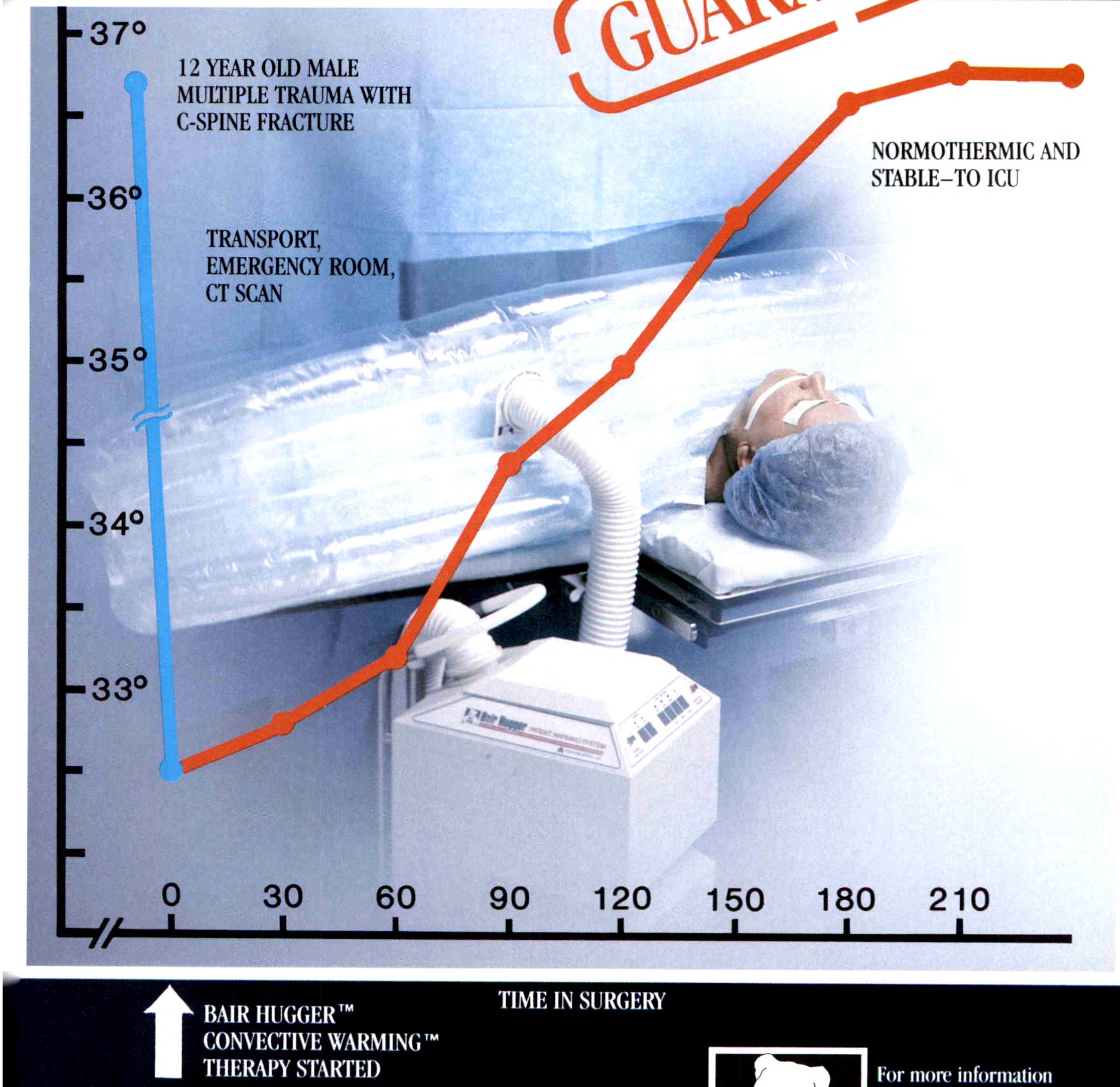

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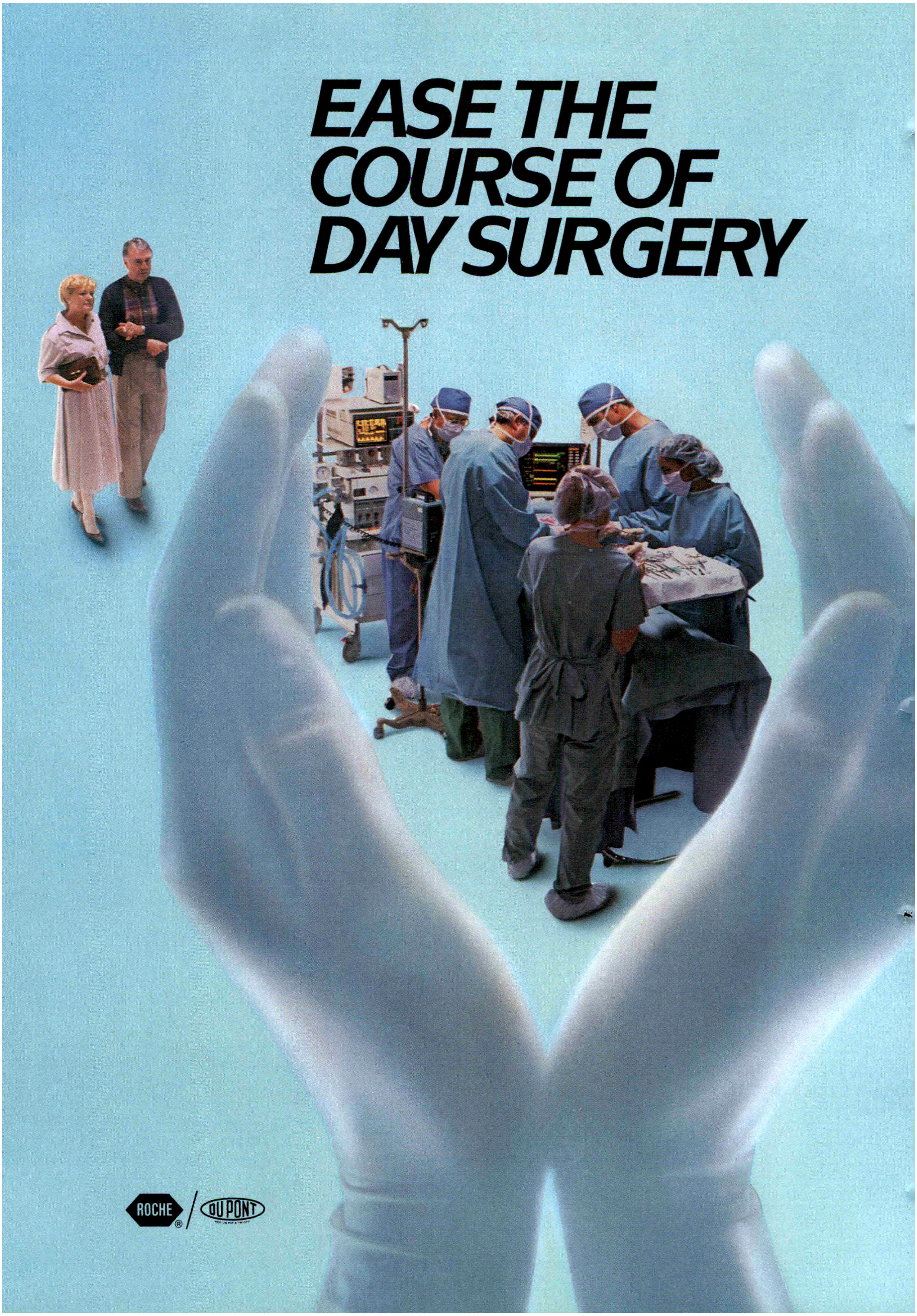
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>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1mg/mL formulation or dilution of the 1mg/mL or 5mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses. Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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Anesthesia Mortality in Perspective

Arthur S. Keats, MD

Key Words: COMPLICATIONS, MORTALITY, MORBIDITY—incidence. MONITORING, SAFETY.

In choosing my topic, I reflected that I started my career in anesthesiology during the period when the Beecher–Todd anesthesia death rate study was in progress (1). This was the first serious attempt to learn the incidence of mortality attributable to anesthesia. At the time I was a resident in Beecher's program. It was his custom to open his office door at 4 PM and serve tea to all trainees and staff who were not working at the time. Discussion during tea could be about any subject except your most interesting case. So during tea I learned about history, prominent personalities, gossip, but also about the problems and anguishes of the mortality study and the controversies surrounding its results (2). It is now about 40 yr later. I seem to be ending my career just as it started, only this time with the Anesthesia Patient Safety Foundation listening to the same anguishes about anesthesia mortality studies. As I listen, I have an uncomfortable feeling that we do not know any more about anesthesia mortality today than we did 40 yr ago. Is is possible that 40 yr of progress in the art and science of anesthesiology, all the research, all the publications, have had no impact on what is considered anesthesia mortality? This sobering thought led to my subject, and I would like to address first the question of whether anesthesia mortality has decreased in the last 40 yr, and then several issues that flow from this one.

Because of my early association with the Beecher–Todd study, I closely followed published literature on this subject. I do not remember encountering data that indicate that anesthesia mortality was decreasing. Despite this, I began to read several years ago that anesthesia mortality was now 1 in 10,000 anesthetics, instead of 3 in 10,000 as reported in the Beecher–Todd study, that it was much better in part because of better patient monitoring, and that it would improve even more as monitoring standards bring all of us into line. Evidence for this optimistic view was apparently a decrease in claims experience for hypoxia in the Harvard Self Insurance Program and the willingness of other insurers to decrease premiums for anyone who promised to use oximeters and capnographs. All this despite reports in the *Wall Street Journal* and *AMA News* that for an unknown reason malpractice claims in all specialties had been decreasing steadily since 1985, and despite the belief of insurance experts that this was only a cycle that would inevitably reverse itself. Then, last fall, in an ultimate display of fatuousness, a panel at the ASA meeting was entitled, "Who Deserves the Credit for the Recent Improvement in Anesthesia Mortality and Morbidity?" Believing that anesthesiologists are not irrational and have a proper respect for evidence, I was incredulous. What decrease? Is this some national euphoria of wishful thinking? We seem to be on a runaway train that will crash as soon as the malpractice claim cycle reverses itself, as plaintiffs' lawyers recover from their temporary problem, whatever it is.

Apparently, this evangelical approach to anesthesia mortality began with a widely quoted article by Davies and Strunin in 1984 (3), who make the following statement in their abstract: "It appears that over the past 30 years the risk of death directly attributable to anesthesia has decreased from 1 in 2680 to about 1 in 10,000." They presented no new data but summarized old data in tabular form listing the risks of anesthesia-related deaths. Of the two most recent studies purportedly documenting this decrease to 1 in 10,000, one comes from England (4) and the other from France (5), both published by 1983, concerning anesthetics given between 1978 and 1982, long before oximeters and monitoring standards.

In 1979 I critically reviewed all the anesthesia mortality studies to that date and pointed out some serious limitations of these studies (6). Since then other excellent reviews (7,8) have been published, reviews that found even more problems than I did, all of which make it impossible to compare results of different studies. These British and French studies

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suffer many of these same problems. But assume they were perfect. Just knowing the differences in anesthesia training programs and certification processes and in hospital environment and medical practice patterns in England and France compared to our own, would you believe their experiences in 1980 apply to the United States in 1989? I cannot make that transition. I believe wishful thinking is the only basis for believing anesthesia mortality today is less than it was 40 yr ago.

How is it that we do not know that anesthesia mortality is different today? There are many good reasons. Here are just a few. First, no anesthesia mortality study has even been attempted in this country since 1973, when Marx et al. (9) published their small experience of about 35,000 patients covering the years 1965–1969. For almost 20 yr, no one has published any data similar to mortality data published before then. Second, our enthusiasts would like to compare a death rate of 3 in 10,000 in 1950 with 1 in 10,000 in 1980 and say that a significant decrease has occurred. Are we talking about the same thing? There are no agreed definitions of what constitutes anesthesia mortality, no agreement as to what to look for and count, no agreement over how much of the perioperative period to include or how many years to cover before practices change too dramatically. Without some agreement as to a uniform method, how can we ever make believable comparisons? These are the same questions that complicate the development of the ASA sponsored effort with the Center for Disease Control in surveying anesthesia mortality. Clearly, some causes of mortality in 1980 must be different from 1950. Consider the patient population, the operations now done, the new drugs and knowledge, and the different environment. Would historical controls have any meaning now? Some of you may remember that in the 1950s a patient with a history of previous myocardial infarction was considered too sick to undergo almost any elective operation because of the hazards of anesthesia. Is it not strange then that for all the cardiac surgery done in the last 20 yr, there are so few deaths ascribed to anesthesia when results of surgical treatment were reported? Is it because there were none in this hazardous population, or is it because we do not know what to count in this new population?

The third reason, and probably the most serious one, is that nobody who has studied anesthesia mortality has ever recorded the events they considered a mortality, as one would in a case report. What Beecher and Todd thought was an anesthetic death in 1950 is now just as mythical as the anesthetic deaths reported in the most recent studies. Instead of events, these studies recorded judgments, what someone thought was a cause of death in the remote past, and that judgment cannot be reviewed in the light of any new knowledge. It is all lost. What remains published are judgments forced into a taxonomy of known causes of deaths or a classification of errors. For more than 30 yr of effort, we have no data except a set of judgments we must take on faith. I have trouble believing that judgments made decades ago represent data. They represent the bias that existed at the time and make no allowance for new knowledge to provide new answers. For example, in 1958 I gave a patient succinylcholine about a week after massive leg injuries. He promptly developed ventricular fibrillation and could not be resuscitated. Soul-searching wisdom at that time said that death was from hypoxia because I had used 80% nitrous oxide during induction. Several years later I read about succinylcholine-induced hyperkalemia in posttraumatic patients.

Dr. Cheney, the scrupulously honest investigator who heads the ASA Closed Claims Study, is beginning to have second thoughts about the judgments that represent the basic data of his study. He reports high interrater reliability in the judgments he collects from his reviewers (10). Why not? We are all brainwashed by the error-blame mentality in reviewing anesthetic records. But even Dr. Cheney now has concerns about reviewers' judgments. He finds that when reviewers are asked their opinion as to the appropriateness of anesthesia care, the answer varies with severity of outcome (11). When brain damage follows an incident, the reviewer is much more likely to find inappropriate care—that is, errors—than if the patient recovers. Furthermore, his Committee is now reviewing cases that only 2 yr ago would have been classified as inadequate ventilation. But now these patients have oximeters in place and they show no desaturation (F. W. Cheney, personal communication). Now it seems that the initial event had to be circulatory, not respiratory. What happens now to all those events previously judged to be inadequate ventilation or esophageal intubation, not to mention all those anesthesiologists crucified in court by these expert judgments? If you still have doubt about the value of judgments, read the testimony of some of our prominent anesthesiologists when they serve as expert witnesses in malpractice actions. You will gain a healthy disrespect for judgments.

Here are three good reasons why we do not know if anesthesia mortality is less today: (a) We have not studied it in 20 yr. (b) We make no allowances for changes in patients and practice over the years. (c) We cannot review previous data because they are only recorded as judgments. If we do not know what actually happened over the past 40 yr, then we can postulate. Here are some postulates:

> Postulate A: *Anesthesia mortality has decreased because of our efforts toward improving anesthesia care.* Why not? We have streamlined anesthesia machines, high-tech monitors, better drugs, and nonflammable anesthetics. We now know all about pharmacodynamics, malignant hyperthermia, anaphylaxis. This seems a reasonable postulate.
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> Postulate B: *Anesthesia mortality has decreased because of the efforts of others in improving medical and surgical care.* Why not? Think about the contribution of closed-chest resuscitation, defibrillators, new cardiovascular drugs, better medical preparation of cardiac, hypertensive, and diabetic patients, new surgical techniques. This too seems reasonable.
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> Postulate C: *Anesthesia mortality has not decreased because most (51%–99%) are caused by errors, and no progress has been made in error reduction.* This is a widely held view that accounts for the great current activity under the aegis of improved patient safety. This too seems plausible.
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> Postulate D: *All of the above are true, but anesthesia mortality has not decreased because we create new mechanisms of mortality at the same rate we solve them.*

This last, I believe, is the most likely possibility. This is not an outlandish hypothesis because we never measured in any systematic way the risks and the benefits of what we consider improvements in anesthetic care. Without these, we can never know whether any innovation solves more problems than it causes. Derivation of risk-benefit estimates is crucial to measurement of progress in all of medicine. It is obvious that if some innovation is designed to prevent a fatal event that occurs 1 in 10,000 anesthetics, we must be sure the innovation does not cause a different but equally fatal event 1 in 10,000 times. Conversely, on the benefit side, how much improved pain relief by epidural narcotics or patient-controlled analgesia is necessary to justify its use, if 1 in 50,000 patients suffers death from respiratory arrest through its use? These difficult questions need answers. I postulate that because we have never systematically measured risks and benefits, we may have actually created new mechanisms for anesthesia mortality.

Let me give you some examples of these possibilities. Operating room ventilators were introduced 30 yr ago to prevent hypoventilation during operation, especially the hypercarbia that was described during unaugmented ventilation in thoracic operations. We then extended mechanical ventilation to all patients because of the wide use of long-acting muscle relaxants. But operating room ventilators caused problems of inadequate ventilation by leaks, open relief valves, disconnection, failure of low pressure alarms, and simple failure to turn the ventilator on. Is is possible that the risks of operating room ventilators far exceed the risk of hypoventilation, or rather hypercarbia? After all, by the measure of trainees who rotate with us from other programs, almost nobody uses nitrous oxide any more. So hypoxia is unlikely even with hypoventilation. Are there any serious risks of hypercarbia? Do you suppose a new standard stating that all apneic patients be hand ventilated would decrease anesthesia mortality because it would eliminate most ventilator-induced problems? Would hand ventilation reduce risks much more than reducing benefits?

Another example. After 1970 we plunged into the narcotic anesthesia era. For the real enthusiasts, their goal, I believe, is total intravenous anesthesia with the benefit of pharmacokinetic modeling and computerized drug administration. Although I understand the intellectual titillation of this approach, I never understood discarding the simple elegance of the lung as a route for drug administration, its ease of dose manipulation, and its complete uniqueness in being able to retrieve a drug at will. Nevertheless, it is rare to see an anesthesia record today that does not include intraoperative administration of a narcotic. The benefit of this practice is greater circulatory stability, a euphemism for less hypotension. The price we pay is an increased incidence of postoperative respiratory arrest, or depression, or asphyxia, because short-acting narcotics turn out to be not so short-acting when given in large doses, and because physicians without knowledge of the narcotics given during an operation prescribe narcotics to be given after the operation. Is there evidence that lesser intraoperative hypotension confers known benefits on the outcome of operation compared to well-documented risks of death or brain damage from narcotic-induced postoperative respiratory arrest? One can also ask whether the benefit of lesser hypotension justifies the lost lives and destroyed careers of anesthesiologists whose narcotic abuse was made possible by participation in this great narcotic anesthesia experiment? I think their lives are also part of the risk of narcotic anesthesia just as both anesthesiologists and patients were part of the risks of explosions by flammable anesthetics.

Let me give you some other risk-benefit examples. How many deaths from hyperkalemia have resulted from potassium infusions to correct preoperative potassium levels not known to be harmful? Nobody bothered to measure the benefits of this practice because the reward was so great. What was the reward? We finally had a way to get even with the surgeon by canceling his operation. With this as a reward, why bother measuring benefits? Similarly, how many deaths occurred from failure to administer in a timely fashion what we perceived as risky vasopressors because of our addiction to the concept that hypotension is in reality hypovolemia and must be treated by water intoxication?

These risk-versus-benefit issues are even clearer if we apply them to monitors because we do not believe monitors can be harmful. Without risks, why even bother measuring benefits? After all, more information simply has to be beneficial. This is why we created monitoring standards without even attempting to measure efficacy, that is, *if they really benefit patients*. However, with a little thought it becomes obvious that monitors are diagnostic tools and the risk of all diagnostic tools, whether x-rays, or laboratory studies, or monitors, is that they are neither 100% sensitive nor 100% specific. In monitoring, as in all diagnostic studies, there is always the risk of false information or false interpretation of correct information that can lead to bad decisions and bad patient consequences. This has been demonstrated many times over.

For example, electronic monitoring of fetal heart rate. The usefulness of this monitor for detection of fetal hypoxia in high-risk obstetric patients is well documented. Based on the no-harm principle, why not apply it to all obstetric patients and detect the rare fetal hypoxia in low-risk patients? At least several well-done studies have now shown that when this is done, the cesarean section rate increases with no improvement in the outcome of the babies (12). Here is an example of a good monitor with a high false-positive rate applied to the wrong group of patients, in such a way that they are needlessly exposed to all the risks of an unnecessary anesthetic and operation.

Another example is the pulmonary artery catheter. The risks of this device in terms of various types of lung trauma are well known and are accepted as worth the risk because of the assumed benefits. However, well-designed studies to measure benefits have been rare. When they were done, a potential for benefit was demonstrated in the mixed population of a medical intensive care unit, but no benefit could be shown for patients in the coronary care unit (13). Now, recently, a study of more than 3000 patients with acute myocardial infarction, some of whom had a pulmonary artery catheter inserted as part of their care, strongly suggests that when patients with equal severity of disease were compared, a 15%–20% excess mortality occurred in the patients with the pulmonary artery catheters (14). A reason for the excess mortality was not identified, but could easily have been from wrong treatment based on false positives or false negatives, or from wrong treatment of correct pressures, because in the presence of myocardial infarction wedge pressure does not measure diastolic volume or compliance of the ventricle, which are the major problems in myocardial infarction. Whatever the cause, the use of a pulmonary artery catheter in this setting may have increased the death rate. These investigators could not even demonstrate a benefit of the catheter in cardiogenic shock.

The above are examples of monitors the limitations of which have not been studied. Let me postulate that our treasured electrocardiogram (ECG) monitoring does more harm than good when used in patients without heart disease. The ECG was introduced into the operating room in the 1950s, when arrhythmias from cyclopropane were important, when cardiac surgery was just starting, and when diagnosis of cardiac arrest was important because open cardiac massage had now become available. We believed ECG monitoring was so successful, we expanded it to all patients, and now it is a standard procedure. We know that arrhythmias, although frequent in healthy patients, are transient, rarely treated, and lead to no bad outcome. In healthy patients, the ECG is now used to count heart rate. So we no longer keep a finger on the pulse. We are also aware that one can have no blood pressure for 3–5 min before heart rate slows or abnormal rhythms appear. Without a finger on the pulse, is it possible the ECG actually contributed to the occurrence of ischemic brain damage? One important use of the ECG is said to be the diagnosis of sudden cardiac arrest. But if the ECG goes flat or wavy lines appear, how often is the first response to check the electrodes, change the electrodes, then send out for a new ECG machine? This really happens. Do you think it reasonable that we could decrease the number of brain-damaged patients by eliminating ECG monitoring except in patients with heart disease? Maybe go back to counting the pulse with a finger? Or, better yet, use the oximeter to measure heart rate and get rid of the ECG. After all, when Jeffrey Cooper tried to demonstrate the efficacy of the oximeter, he found it most useful for identifying what he called hypovolemia and hypotension (15).

Let me postulate the same thing for the automated blood pressure recorder. I cannot explain its popularity because it is a treacherous instrument. It was introduced to ensure that our nonvigilant anesthesiologists take the blood pressure at least every 5 min. So we have an apparatus that always displays a good blood pressure whenever you look at it for 2 or 4 min after it was taken. Suppose that right after a 120/80 mm Hg reading, the blood pressure disappears. Now no systemic pressure is present for 2–4 min. The next reading, after one more minute, is 0/0. What is the usual response? Punch the manual. Another 45 s. Now it says zero over zero. Next response, get out regular blood pressure cuff and/or send out for another machine. Only then do we believe there is no blood pressure. How many minutes have lapsed without circulation? Do you think this has any relationship to brain damage after successful resuscitation? I did not invent this scenario either.

Let us look at the oximeter. It is a great instrument. But we made it part of our monitoring standards without demonstration of its efficacy. Efficacy cannot be measured in terms of frequency of oxygen desaturation. When you do not measure oxygen saturation and then begin to use an apparatus that measures it, you are obviously going to find a lot of desaturation of which you were unaware. But this is not efficacy. Efficacy means that discovering oxygen desaturation leads to some improved patient outcome. Suppose we treat all patients whose saturation decreases below 90%, as we do now. But suppose, in reality, saturations above 80% lead to no bad outcome. Think of all the patients who will be treated unnecessarily when saturation is less than 90% but more than 80%. At what risk? We do not know, because we have not studied it. Without this information I can envision a subpopulation of this country walking around without their front teeth because of urgent intubation when an oximeter read less than 90%. Unfortunately, making a monitor part of the standard of care guarantees that the experiment necessary to document its benefits will never be carried out because we have ruled out a control group. This is the great drawback of standards. We simply shut the door on measuring efficacy.

By now you undoubtedly think that this is all hyperbole, and that this just cannot be true. Quite honestly, I might have trouble believing it myself, had we not as a specialty engaged in exactly this type of uncritical hysterical behavior with regard to scavenging systems. This was another runaway train, like that of monitoring standards and, now, wishful thinking about anesthesia mortality.

You remember that because operating room pollution was such an urgent problem, we could not wait for proof of toxicity. We were endangering lives of operating room personnel. We were being poisoned. We would develop cancer or have deformed babies. So we urgently created scavenging systems. We got the federal government to declare "safe levels" for something not known to be toxic. We got the Joint Commission on Accreditation of Healthcare Organizations to require testing and record keeping, even though we do not know what the numbers mean. Now, with all the data in, there is no demonstrated toxicity except perhaps an increased incidence of spontaneous abortion. Even data on this point alone are equivocal.

For this, we created a standard of no demonstrated benefit to operating room personnel, no benefit to patients, and well-documented hazards to patients in terms of malfunctions of the scavenging system. By what system of ethics do we continue to use an apparatus that can clearly harm patients for no known benefit to anyone? By what system of ethics, in this day of patients' rights, did we never think it necessary to ask a patient to consent to their increased risk by using a scavenging system for an undocumented benefit to the anesthesiologist, not the patient? We have acted with scavenging systems as we have acted with monitoring standards and now with anesthesia mortality. It seems we cannot wait for the information we need to make secure decisions.

One has to wonder why we behave this way. Why it is we cannot wait for reasonable answers before going off half-cocked, full-steam-ahead to fight dragons and cure problems not known to exist? For example, why are we so anxious to condemn isoflurane in patients with coronary artery disease because it may cause coronary steal? Why are we so anxious to condemn nitrous oxide despite 150 yr of use as a safe drug? Why are we now so anxious to eliminate glucose from intravenous solutions based on a highly controversial relationship to the extent of brain damage after strokes? We seem to want someone to give us strict do's and don'ts, whether right or wrong.

I believe we act this way because we love dogma and the comfort it brings. We have great difficulty saying "I don't know" because it discomfits us. Each time we say it, it removes us one more step from the omniscient authoritative figure we all aspire to be. I do not think that we are different from other specialists in this regard. If internists could say "I don't know," it would not have required Polly Murray, a Connecticut housewife, to doubt 20 doctors and discover Lyme disease all on her own. Even psychiatrists in their current Mindlessness versus Brainlessness debate seem to have the same problem. One very recently wrote, "Psychiatry seems to suck in partial ideas from many sciences as if it were a vacuum abhorring itself, which in itself is not deplorable. But accepting each idea as a fact and quickly making a fashion of its application without testing or validation is detrimental even to an applied science" (16). They, too, have trouble saying "I don't know."

To return to anesthesia mortality, I believe that we have a special problem in saying "I don't know" because that is equivalent to ascribing the event to an act of God. But why not, if act of God means that within the limits of current knowledge we do not know the cause? In my years of practice, I have witnessed many spectacular triumphs as well as catastrophes, both inexplicable in terms of current knowledge. In fact, in most medicolegal events that I review I frankly cannot identify the cause and cannot pigeonhole it in some convenient error-blame taxonomy. In these cases, I am more struck, however, with the inadequate response of the anesthesiologist to any catastrophe whatever or whoever caused it. I often wonder if our error-blame bias doesn't make outcomes of catastrophes worse. Because these events are so rare, I wonder if the usual response of the anesthesiologist is not simple incredulity. He was taught that all anesthetic catastrophes are preventable and the result of error. I wonder if his first thoughts are "this just can't be happening," "some monitor must be wrong," "this is all a mistake." He then proceeds with a confused, irrational, inadequate response to what may be a completely retrievable situation. I often wonder if anesthesia outcomes would improve if we taught that we were not omniscient, that there were unknowns, if we taught that all adverse events were not error and preventable, that some portion of catastrophes were attributable to Syndrome Z of unknown cause—but also that an immediate response, for example, immediate cardiopulmonary resuscitation, would probably rectify the situation. Do you suppose that if we started cardiopulmonary resuscitation on first suspicion of Syndrome Z and perhaps did it three times more often than necessary we could shorten this period of incredulity and error-searching and actually decrease the number of brain-damaged patients without ever having to discover an error? Our statistics would show a threefold increase in cardiac arrest because cardiopulmonary resuscitation was given. But perhaps the number of brain-damaged survivors would decrease threefold.

Let me return to where I started. We have a vague estimate of the incidence of catastrophic outcomes of anesthesia that we describe as anesthesia mortality. But we have no evidence that it is getting better or worse. More distressing to me is that for all our voluminous publications we have not measured the results of what we believe to be the enormous progress made over the past 40 yr. I have no enthusiasm at all for more massive studies looking for errors as have been done in the past. I do have enthusiasm for documenting progress in anesthesiology by defining and studying subsets of patients who receive anesthetics, by stratifying these populations carefully, and by grading the outcomes of anesthesia. If we better define what we are looking for, if we measure graded outcomes rather than simply counting, and if we undertake these studies with sound statistical advice, I believe we can succeed. To some degree, we are doing it now with obstetrical patients, patients with coronary artery disease, neurosurgical operations, and patients with hip fractures. We are obtaining good, new information that suggests improvements in care. But we need to do this more than sporadically if we are to document progress. I believe we have a great future in well-designed clinical research aimed at defining the role of anesthesia in surgical mortality rather than what we have done in the past, the counting of the anesthesia mortality in terms of accidents, errors, and blames.

Finally, I believe that we must accept the possibility that some things we do in the name of improving anesthesia care may actually be associated with hazards that are equal to or greater than any benefits derived. Unless we accept the necessity of both measuring benefits and substituting these measures for enthusiasm, logic, intuition, wishful thinking, or runaway trains, unless we systematically measure hazards in relation to benefits instead of reporting the occasional adverse result, and unless we view all innovations in this light, we will never know, for all our technical sophistication, if we are improving the outcomes of anesthesia care. This is my message.

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ologists take the blood pressure at least every 5 min. So we have an apparatus that always displays a good blood pressure whenever you look at it for 2 or 4 min after it was taken. Suppose that right after a 120/80 mm Hg reading, the blood pressure disappears. Now no systemic pressure is present for 2–4 min. The next reading, after one more minute, is 0/0. What is the usual response? Punch the manual. Another 45 s. Now it says zero over zero. Next response, get out regular blood pressure cuff and/or send out for another machine. Only then do we believe there is no blood pressure. How many minutes have lapsed without circulation? Do you think this has any relationship to brain damage after successful resuscitation? I did not invent this scenario either.

Let us look at the oximeter. It is a great instrument. But we made it part of our monitoring standards without demonstration of its efficacy. Efficacy cannot be measured in terms of frequency of oxygen desaturation. When you do not measure oxygen saturation and then begin to use an apparatus that measures it, you are obviously going to find a lot of desaturation of which you were unaware. But this is not efficacy. Efficacy means that discovering oxygen desaturation leads to some improved patient outcome. Suppose we treat all patients whose saturation decreases below 90%, as we do now. But suppose, in reality, saturations above 80% lead to no bad outcome. Think of all the patients who will be treated unnecessarily when saturation is less than 90% but more than 80%. At what risk? We do not know, because we have not studied it. Without this information I can envision a subpopulation of this country walking around without their front teeth because of urgent intubation when an oximeter read less than 90%. Unfortunately, making a monitor part of the standard of care guarantees that the experiment necessary to document its benefits will never be carried out because we have ruled out a control group. This is the great drawback of standards. We simply shut the door on measuring efficacy.

By now you undoubtedly think that this is all hyperbole, and that this just cannot be true. Quite honestly, I might have trouble believing it myself, had we not as a specialty engaged in exactly this type of uncritical hysterical behavior with regard to scavenging systems. This was another runaway train, like that of monitoring standards and, now, wishful thinking about anesthesia mortality.

You remember that because operating room pollution was such an urgent problem, we could not wait for proof of toxicity. We were endangering lives of operating room personnel. We were being poisoned. We would develop cancer or have deformed babies. So we urgently created scavenging systems. We got the federal government to declare "safe levels" for something not known to be toxic. We got the Joint Commission on Accreditation of Healthcare Organizations to require testing and record keeping, even though we do not know what the numbers mean. Now, with all the data in, there is no demonstrated toxicity except perhaps an increased incidence of spontaneous abortion. Even data on this point alone are equivocal.

For this, we created a standard of no demonstrated benefit to operating room personnel, no benefit to patients, and well-documented hazards to patients in terms of malfunctions of the scavenging system. By what system of ethics do we continue to use an apparatus that can clearly harm patients for no known benefit to anyone? By what system of ethics, in this day of patients' rights, did we never think it necessary to ask a patient to consent to their increased risk by using a scavenging system for an undocumented benefit to the anesthesiologist, not the patient? We have acted with scavenging systems as we have acted with monitoring standards and now with anesthesia mortality. It seems we cannot wait for the information we need to make secure decisions.

One has to wonder why we behave this way. Why it is we cannot wait for reasonable answers before going off half-cocked, full-steam-ahead to fight dragons and cure problems not known to exist? For example, why are we so anxious to condemn isoflurane in patients with coronary artery disease because it may cause coronary steal? Why are we so anxious to condemn nitrous oxide despite 150 yr of use as a safe drug? Why are we now so anxious to eliminate glucose from intravenous solutions based on a highly controversial relationship to the extent of brain damage after strokes? We seem to want someone to give us strict do's and don'ts, whether right or wrong.

I believe we act this way because we love dogma and the comfort it brings. We have great difficulty saying "I don't know" because it discomfits us. Each time we say it, it removes us one more step from the omniscient authoritative figure we all aspire to be. I do not think that we are different from other specialists in this regard. If internists could say "I don't know," it would not have required Polly Murray, a Connecticut housewife, to doubt 20 doctors and discover Lyme disease all on her own. Even psychiatrists in their current Mindlessness versus Brainlessness debate seem to have the same problem. One very recently wrote, "Psychiatry seems to suck in partial ideas from many sciences as if it were a vacuum abhorring itself, which in itself is not deplorable. But accepting each idea as a fact and quickly making a fashion of its application without testing or validation is detrimental even to an applied science" (16). They, too, have trouble saying "I don't know."

To return to anesthesia mortality, I believe that we have a special problem in saying "I don't know" because that is equivalent to ascribing the event to an act of God. But why not, if act of God means that within the limits of current knowledge we do not know the cause? In my years of practice, I have witnessed many spectacular triumphs as well as catastrophes, both inexplicable in terms of current knowledge. In fact, in most medicolegal events that I review I frankly cannot identify the cause and cannot pigeonhole it in some convenient error-blame taxonomy. In these cases, I am more struck, however, with the inadequate response of the anesthesiologist to any catastrophe whatever or whoever caused it. I often wonder if our error-blame bias doesn't make outcomes of catastrophes worse. Because these events are so rare, I wonder if the usual response of the anesthesiologist is not simple incredulity. He was taught that all anesthetic catastrophes are preventable and the result of error. I wonder if his first thoughts are "this just can't be happening," "some monitor must be wrong," "this is all a mistake." He then proceeds with a confused, irrational, inadequate response to what may be a completely retrievable situation. I often wonder if anesthesia outcomes would improve if we taught that we were not omniscient, that there were unknowns, if we taught that all adverse events were not error and preventable, that some portion of catastrophes were attributable to Syndrome Z of unknown cause—but also that an immediate response, for example, immediate cardiopulmonary resuscitation, would probably rectify the situation. Do you suppose that if we started cardiopulmonary resuscitation on first suspicion of Syndrome Z and perhaps did it three times more often than necessary we could shorten this period of incredulity and error-searching and actually decrease the number of brain-damaged patients without ever having to discover an error? Our statistics would show a threefold increase in cardiac arrest because cardiopulmonary resuscitation was given. But perhaps the number of brain-damaged survivors would decrease threefold.

Let me return to where I started. We have a vague estimate of the incidence of catastrophic outcomes of anesthesia that we describe as anesthesia mortality. But we have no evidence that it is getting better or worse. More distressing to me is that for all our voluminous publications we have not measured the results of what we believe to be the enormous progress made over the past 40 yr. I have no enthusiasm at all for more massive studies looking for errors as have been done in the past. I do have enthusiasm for documenting progress in anesthesiology by defining and studying subsets of patients who receive anesthetics, by stratifying these populations carefully, and by grading the outcomes of anesthesia. If we better define what we are looking for, if we measure graded outcomes rather than simply counting, and if we undertake these studies with sound statistical advice, I believe we can succeed. To some degree, we are doing it now with obstetrical patients, patients with coronary artery disease, neurosurgical operations, and patients with hip fractures. We are obtaining good, new information that suggests improvements in care. But we need to do this more than sporadically if we are to document progress. I believe we have a great future in well-designed clinical research aimed at defining the role of anesthesia in surgical mortality rather than what we have done in the past, the counting of the anesthesia mortality in terms of accidents, errors, and blames.

Finally, I believe that we must accept the possibility that some things we do in the name of improving anesthesia care may actually be associated with hazards that are equal to or greater than any benefits derived. Unless we accept the necessity of both measuring benefits and substituting these measures for enthusiasm, logic, intuition, wishful thinking, or runaway trains, unless we systematically measure hazards in relation to benefits instead of reporting the occasional adverse result, and unless we view all innovations in this light, we will never know, for all our technical sophistication, if we are improving the outcomes of anesthesia care. This is my message.

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Additive Contribution of Nitrous Oxide to Halothane MAC in Infants and Children

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MURRAY DJ, MEHTA MP, FORBES RB, DULL DL. Additive contribution of nitrous oxide to halothane MAC in infants and children. Anesth Analg 1990;71:120–4.

Fifty-one infants and small children (14.7 ± 7.2 mo) were studied to determine the MAC of halothane in O_2 (n = 11) and in the presence of three different nitrous oxide (N_2O) concentrations (25% [n = 13], 50% [n = 13], and 75% [n = 14]).

In the three N_2O groups, after randomly assigning patients to an N_2O group, anesthesia was induced with halothane and N_2O using a pediatric circle system. After endotracheal intubation, halothane and N_2O end-expired concentrations were adjusted to predetermined concentrations. The initial halothane concentrations in each group were based on the assumption that each percent N_2O reduced halothane concentrations by 0.01 vol % (assumed halothane MAC = 1.0 vol %). Based on the response of the preceding subject in each group, halothane concentrations were increased or decreased depending on whether the response was to move or not to move, respectively, in response to the surgical incision. The mean duration of constant end-tidal concentrations before skin incision was 10 min. End-tidal gases were sampled and measured from a separate distal sampling port of an endotracheal tube during controlled ventilation (Perkin-Elmer Mass Spectrometer).

The MAC value for halothane in O_2 was 0.94 ± 0.08 vol % (mean ± SD). The MAC values of halothane in the presence of 25%, 50%, and 75% N_2O were 0.78 ± 0.12 vol %, 0.44 ± 0.10 vol %, and 0.29 ± 0.06 vol %, respectively. All concentrations of N_2O significantly reduced the MAC of halothane. A regression analysis through all four data points yielded a linear relationship (r^2 = 0.87) with a predicted MAC for N_2O of 105 vol %.

Unlike halothane and isoflurane, the predicted MAC of N_2O in infants and children is similar to that reported by others in adults. Similar to the results of clinical studies in adults, the contribution of N_2O to halothane MAC in children is additive.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHESIA, PEDIATRIC. POTENCY, ANESTHETIC—nitrous oxide. INTERACTIONS (DRUG), NITROUS OXIDE, HALOTHANE.

In clinical studies, when two anesthetic drugs are combined anesthetic requirements for both drugs are reduced in a simple additive fashion (1–5). Recently, it has been observed that different nitrous oxide (N_2O) concentrations may not contribute to enflurane MAC in an additive manner (6). In a rat model, Cole et al. found concentrations of 10%–30% N_2O reduced enflurane MAC relatively more than concentrations of 60%–80% N_2O. Using multiple N_2O concentrations, the study suggested a nonlinear contribution of N_2O to enflurane MAC (6). In humans, most studies that concluded that the contribution of N_2O to MAC is additive have assessed only one N_2O concentration (3,7). In a study of adults, the effect of two different N_2O concentrations in reducing enflurane MAC suggested a similar additive effect in reducing the MAC of enflurane (8). A clinical study measuring the contribution of multiple N_2O concentrations to halothane, isoflurane, or enflurane in humans is not currently available.

Although absolute MAC values for N_2O in separate age groups are not available, the predicted MAC value of N_2O was lower in older adults than in younger adults in a study assessing the contribution of 60% N_2O in reducing the MAC of isoflurane (7). Age alters anesthesia requirements for halothane and isoflurane (9–11). With the increased MAC of halothane and isoflurane in infants and children, perhaps the contribution of N_2O to halothane anesthesia may be less in this age group than in adults.

The purpose of this study was to measure whether anesthetic requirements for N_2O, like halothane and

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isoflurane, vary with age, and to determine whether the contribution of various concentrations of N_2O reduce halothane MAC requirements in a linear or nonlinear fashion in infants and small children.

Methods

After the study was approved by the Committee for Human Studies and informed written parental consent was obtained, 51 ASA physical status I or II infants and small children (7–30 mo old) who required elective surgery were studied. The infants and small children received no premedicants and fasted for 4–6 h before anesthesia induction. In all infants and children anesthesia was induced by mask with halothane and N_2O using a semi-closed circle system. Oxygen saturation, blood pressure, and heart rate by electrocardiogram were monitored during induction and maintenance of anesthesia. Under deep halothane anesthesia, the tracheas were intubated using a 4.0 or 4.5 Sheridan $Etco_2$ uncuffed tracheal tube, which contains a secondary lumen for obtaining gas samples from the distal end of the endotracheal tube. End-tidal and inspired anesthetic concentrations were measured using a Perkin-Elmer mass spectrometer. After endotracheal intubation, anesthetic concentrations were reduced to predetermined N_2O and halothane concentrations and maintained constant for as long as possible before skin incision. Ventilation was controlled with tidal volumes of 10–12 mL/kg and respiratory rates were maintained between 16 and 24 breaths/min to maintain end-tidal Pco_2 at 32 ± 5 mm Hg (mean ± SD).

The 51 patients were divided into four groups according to the predetermined N_2O concentration used during the study period. The first 40 patients were randomly assigned to either 25% (n = 13), 50% (n = 13), or 75% (n = 14) N_2O groups. The 0% N_2O group (n = 11) was studied after the completion of the N_2O groups. With a constant level of N_2O maintained in each patient, a single halothane concentration was then assessed to determine each child's response to skin incision.

The technique used to determine MAC was adapted from prior MAC studies where the objective was to bracket an end-tidal concentration of halothane that was MAC for the group being studied (3,7–11). Each patient was observed for purposeful movement in the 20–30 s after skin incision. Increases in respiratory rate, coughing, or breath holding after skin incision were not considered to constitute purposeful movement. The initial halothane concentration selected in each group was based on the assumption that 1% N_2O would reduce halothane concentrations by 0.01 vol % because prior studies have determined the MAC of halothane to be 1.0 vol % in infants and children (10). For each subsequent patient, the halothane concentration selected was based on the response of the previous infant or child. The end-tidal halothane concentration was increased or decreased by 0.1 or 0.2 vol % depending on whether the preceding infant or small child studied had moved or not moved after skin incision. A requirement for beginning data collection in a group was an initial paired response of move/no move or vice versa.

The data were analyzed by the method described by Dixon for determining quantal responses (12). The age, weight, CO_2, duration of constant end-tidal values, and halothane MAC were analyzed by one-way analysis of variance to determine differences between the four groups. A regression analysis was applied to the halothane groups to determine the correlation between halothane doses at different N_2O concentrations. All results are expressed as mean ± SD.

Results

The MAC value for halothane in O_2 was 0.94 ± 0.08 vol %. The addition of 25% N_2O reduced the MAC value for halothane to 0.78 ± 0.12 vol %. The MAC value of halothane during 50% and 75% N_2O was 0.44 ± 0.10 and 0.29 ± 0.06 vol %, respectively. The MAC values for halothane were significantly different in each N_2O level and, as expected, increasing N_2O concentrations progressively reduced anesthetic requirements for halothane.

The age, weight, mean expired N_2O concentration, and end-tidal CO_2 are presented in Table 1. Tracheal intubation performed under deep halothane anesthesia occurred a minimum of 15 min and a maximum of 52 min before the assessment of MAC after skin incision. The mean respiratory rate of the infants and children before skin incision was 22.6 ± 3 breaths/min. The mean duration of constant end-expired halothane levels was 10 min (range, 6–27 min). The ratio between end-expired halothane and inspired halothane was 0.96 ± 0.03 at the time of skin incision. The move/no move responses to skin incision of the infants and children at each study level are presented in Figure 1.

Regression analysis was applied to determine the correlation coefficient and slope of the line extrapolated through the data sets. The r value for this line is

Table 1. Summary of Results in Each Group

Age (mo)	Weight (kg)	Response to skin incision: Move (*n*)	Response to skin incision: No move (*n*)	Mean expired N_2O (vol %)	Halothane MAC (vol %)	End-tidal CO_2 (mm Hg)
14.4 ± 6.9	9.9 ± 2.5	6	5	0 (*n* = 11)	0.94 ± 0.08	29.9 ± 3.5
11.5 ± 6.0	9.4 ± 2.0	6	7	24.8 ± 1.4 (*n* = 13)	0.78 ± 0.12	30.4 ± 4.5
15.7 ± 6.4	11.1 ± 2.2	6	7	49.9 ± 1.4 (*n* = 13)	0.44 ± 0.10	29.3 ± 3.0
17.2 ± 6.9	11.2 ± 2.5	7	7	73.3 ± 2.8 (*n* = 14)	0.29 ± 0.06	33.4 ± 3.9

All results are expressed as mean ± SD.

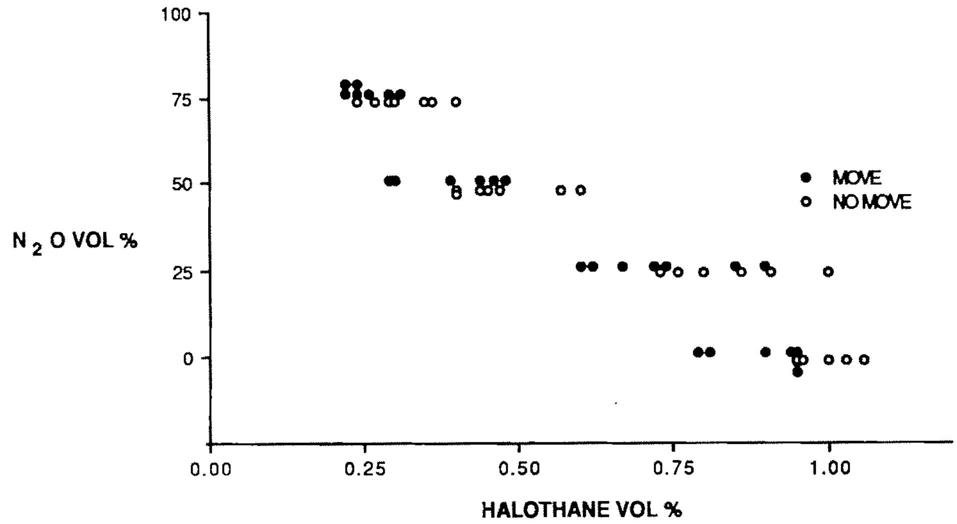

Figure 1. Response to skin incision (move or no move) in four groups of infants assessed at various halothane concentrations. Each patient is represented by a *closed* (move) or *open* (no move) *circle*.

0.934 with an r^2 value of 0.87 (Figure 2). The value for 1 MAC N_2O predicted from extending the linear regression line is 105% (Figure 2).

Discussion

End-expired halothane concentrations were used to reflect central nervous system concentrations of halothane (13,14). The measurement of end-expired halothane assumes that these concentrations reflect end-tidal anesthetic levels. Arterial anesthetic concentrations were assumed to be equivalent to levels of halothane in the central nervous system.

For halothane concentrations: end-expired $\propto$ end-tidal $\propto$ alveolar $\propto$ arterial $\propto$ central nervous system.

Entrainment of inspired gas could limit the accuracy of end-tidal values in reflecting alveolar halothane concentration, particularly when respiratory rates are rapid and tidal volumes are small. For this reason, distal tracheal gas sampling from an endotracheal tube in infants was used to measure alveolar gas samples (15,16). Alveolar anesthetic levels reach equilibrium with anesthetic levels in the brain over a period of time. A soluble anesthetic such as halothane requires more time to achieve equilibrium with vessel-rich tissue groups than does N_2O. In infants the time constant of equilibrium for halothane concentrations in the central nervous system to reach equilibrium with end-tidal halothane concentrations is shorter than in adults (14). A minimum of two to three constants would be required to assure that brain concentrations are equivalent to alveolar levels (13,14). Before the assessment of MAC, anesthetic concentrations were unchanged for a period of time equivalent to three to four time constants (10 min). Tracheal intubation was performed under deeper levels of halothane anesthesia without muscle relaxants, and then halothane concentrations were reduced to the end-tidal halothane concentrations that

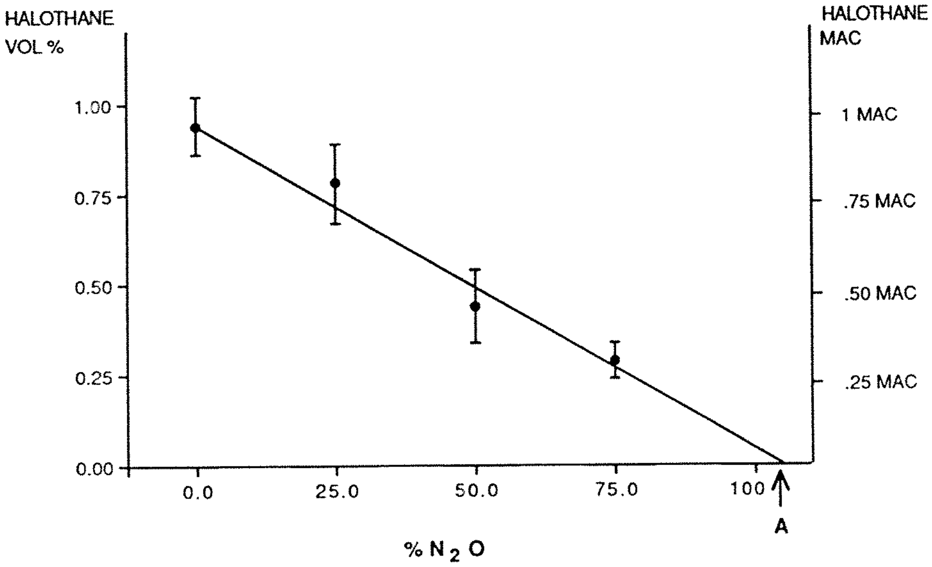

Figure 2. Regression analysis of four data points. The halothane MAC at different N_2O concentrations are plotted, and the line represents the regression analysis through all four data points. "A" indicates predicted MAC of N_2O.

were assessed at skin incision. For this reason, small differences between alveolar and inspired halothane concentrations were measured at the time of skin incision (13).

The MAC of halothane in this study was similar to the values reported by Gregory et al. in a study of infants of similar age (10). In prior studies in adults, when N_2O was added to halothane, enflurane, or isoflurane the contribution to MAC was additive (3,7,8). We found a similar additive effect at three N_2O concentrations (25%, 50%, and 75%) during halothane anesthesia. When six different concentrations of N_2O were assessed, Cole et al. suggested that higher N_2O concentrations (60%–80%) contributed proportionately less to the MAC of enflurane in rats than lower concentrations (10%–30%) (6). In an editorial that accompanied this article, Eger suggested the data presented by Cole et al. could have been interpreted to indicate an additive effect of N_2O (1).

In a letter to the editor, Cole et al. suggest that perhaps higher N_2O concentrations by increasing sympathetic activity may alter anesthetic requirements (17). If increases in sympathetic activity during N_2O are dose-related, as suggested in clinical studies, and if increases in sympathetic stimulation increase anesthetic requirements, then a nonlinear contribution of N_2O might occur with lower N_2O concentrations reducing MAC proportionately more than higher N_2O concentrations. In infants and children, Hickey et al. and Murray et al. found cardiovascular changes that suggest minimal sympathetic stimulating effect of N_2O (18,19). This may explain why a linear contribution of N_2O was observed in this study of infants and children but not in the study of Cole et al. A separate clinical study would be required to assess whether increases in sympathetic activity produced by N_2O alter anesthetic requirements.

With requirements for halothane and isoflurane concentrations increased 130% and 140% in infants compared to adults, we anticipated that the MAC of N_2O might be increased in infants and children, and that the contribution of N_2O to halothane anesthesia would be less than in adults. Using a linear regression analysis, the projected N_2O concentration required to produce 1.0 MAC in infants and small children was 105%. In adults, using assessments based on the additive contribution of a single N_2O concentration to halothane or isoflurane, the MAC of N_2O was predicted to be 108%, 118%, 105%, and 110% (3,7,8). The predicted MAC of N_2O in this study as well as in prior clinical studies assumes that the contribution of N_2O to MAC remains linear at concentrations of greater than 75%. In the only study assessing the MAC of N_2O alone under hyperbaric conditions, the MAC of N_2O in healthy adult volunteers was 106% (20).

Although this study supports the concept of additivity of anesthetic agents in predicting MAC, we found that the MAC of N_2O, unlike the volatile anesthetics, was not increased in infants and small children. In a younger (19–30 yr), as well as in an older patient population (>55 yr), the predicted MAC of N_2O during isoflurane anesthesia decreased from 116% to 100% (7). The MAC of halothane in O_2 in infants was 0.94 vol % compared to 0.78 vol % in adults. The addition of 75% N_2O to halothane reduced the MAC of halothane to 0.29 ± 0.06 vol % in infants and children. In adults, the MAC of halothane during 70% N_2O is 0.29 vol % (3). When combined with the other properties of N_2O, such as its low solubility and minimal cardiovascular effects, the continued use of N_2O in children seems warranted because N_2O reduces halothane and perhaps isoflurane concentrations required to achieve surgical anesthesia to a greater degree in infants than in adults.

In summary, in infants and children, N_2O concentrations reduce halothane MAC in a linear additive manner. The predicted MAC of N_2O based on a linear regression analysis is similar in infants and adults.

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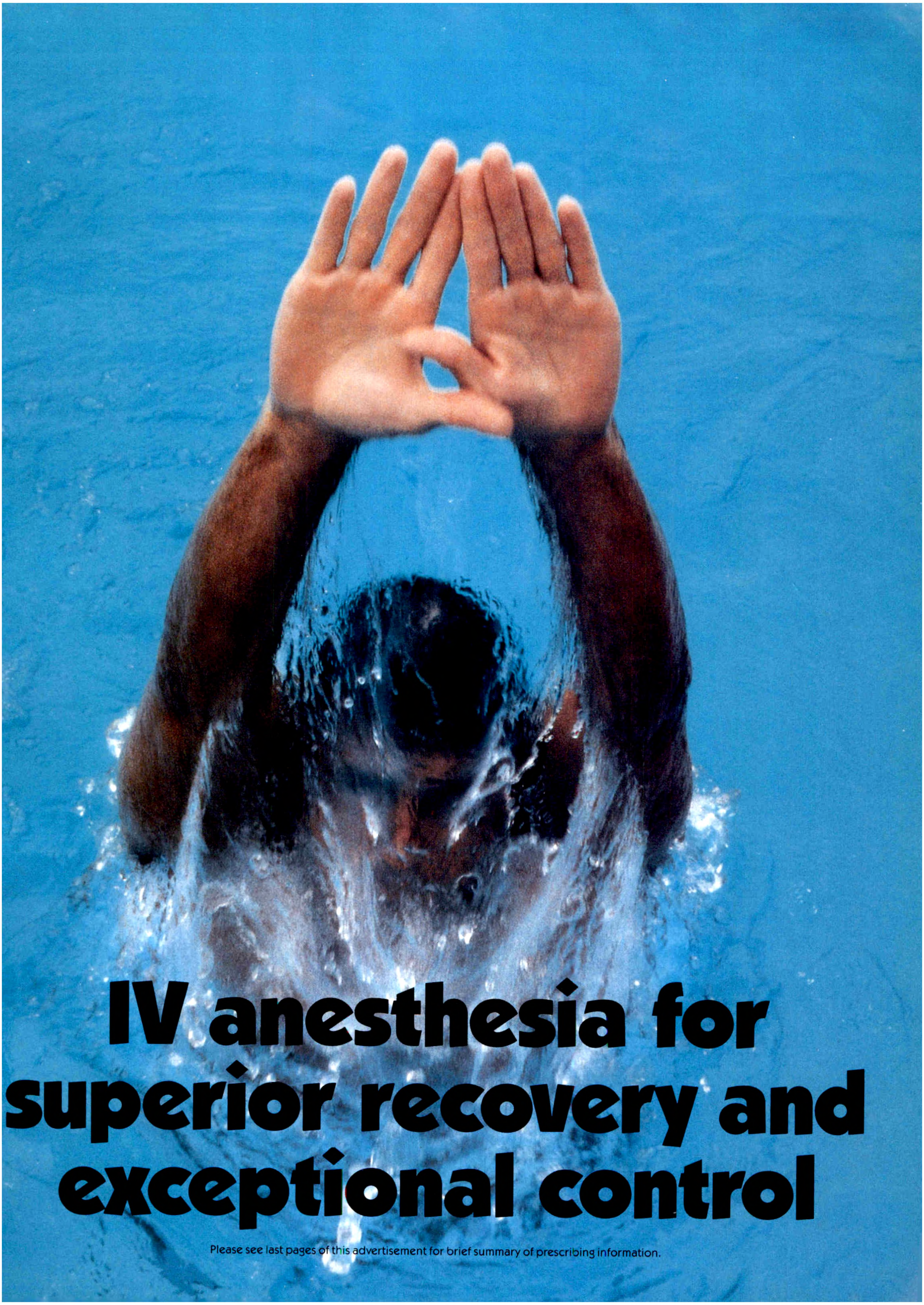

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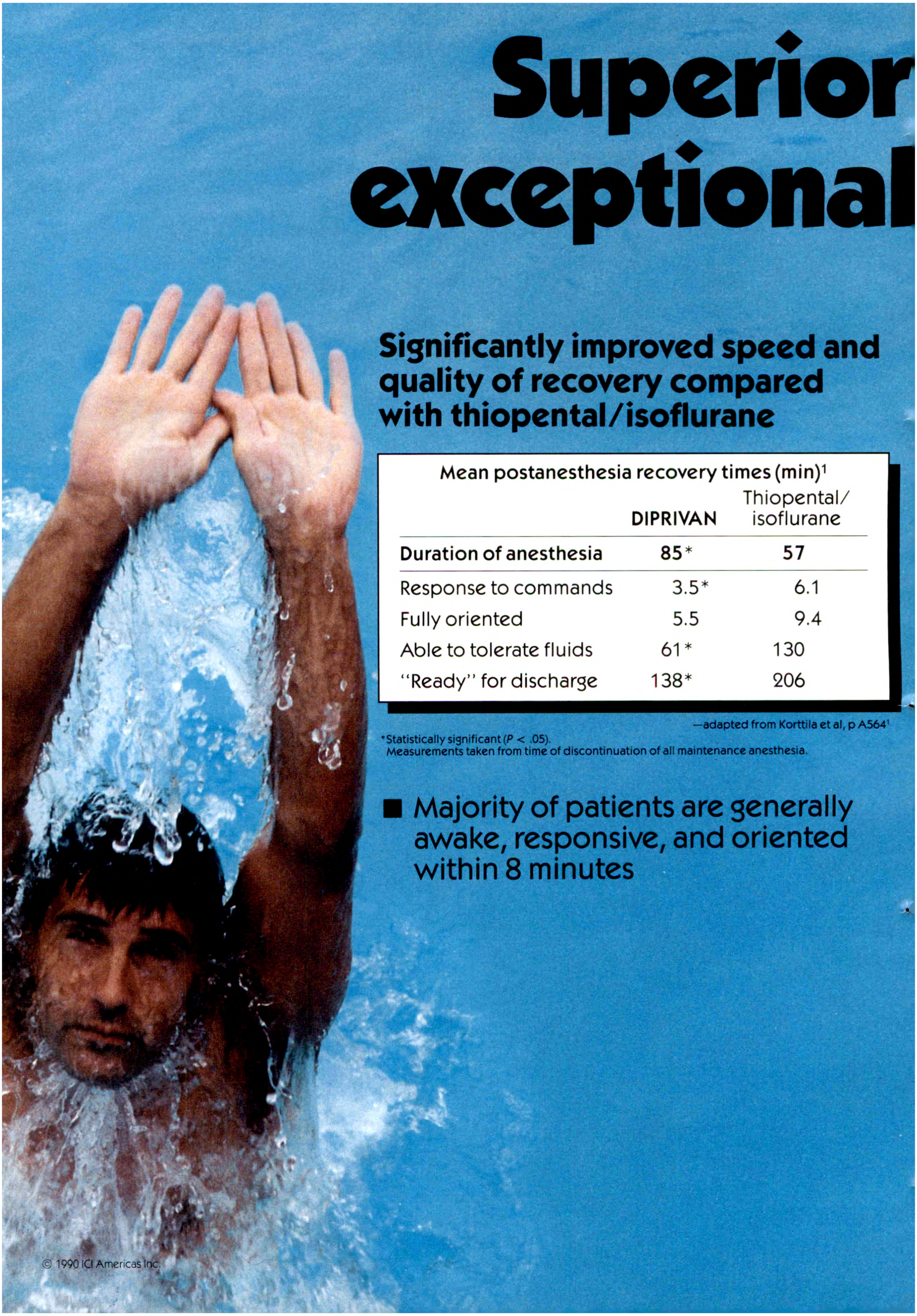

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Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

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recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

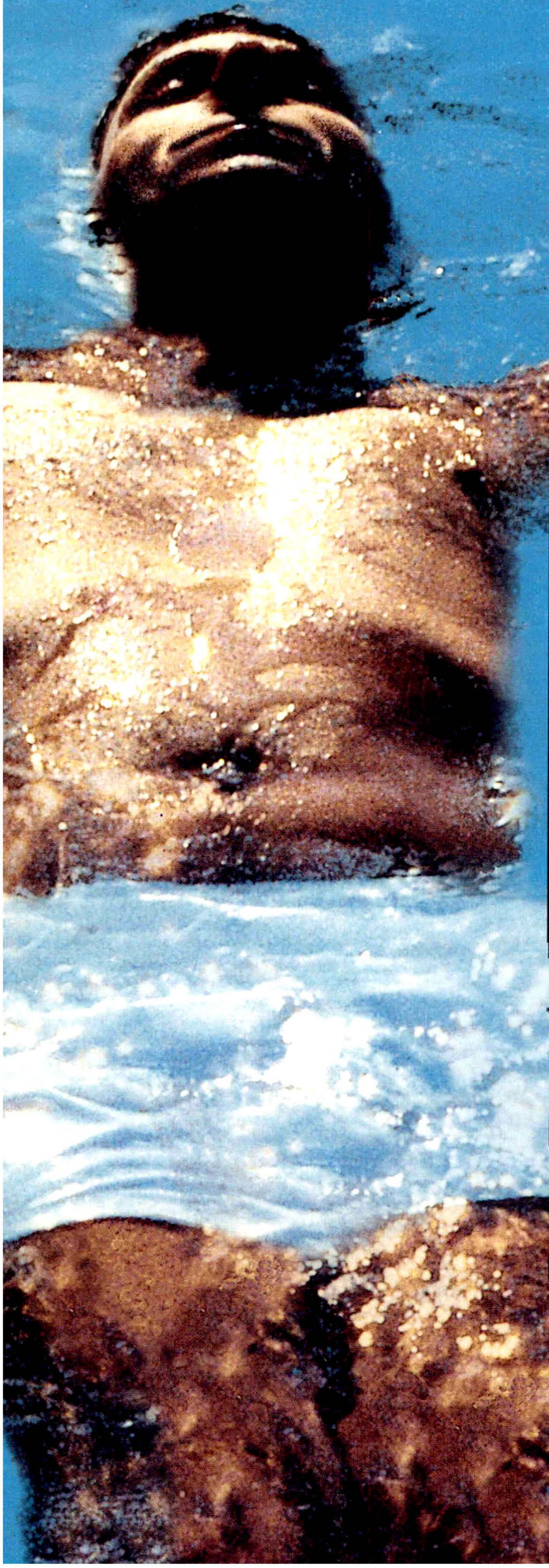
For induction and maintenance

DIPRIVAN®

INJECTION

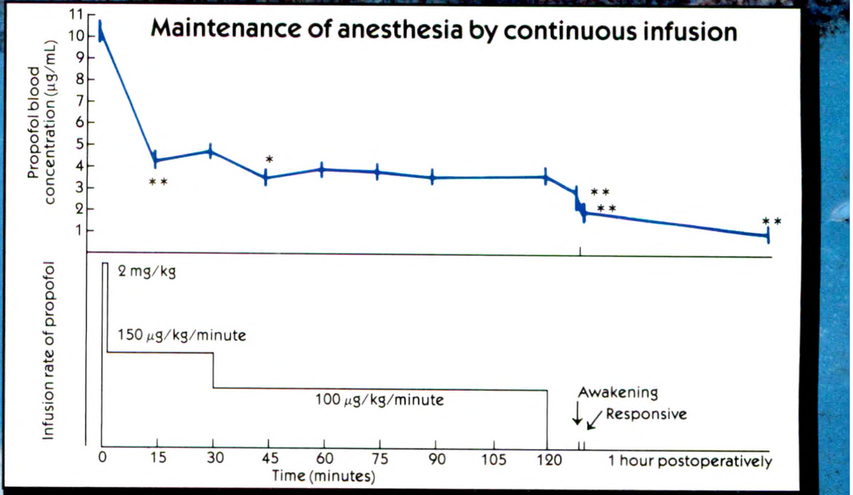
propofol

Superior exceptional



Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 μg/kg/min for 30 minutes—then 100 μg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®
INJECTION
propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: **1.** Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. **2.** Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. **3.** Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. **4.** Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. **5.** Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

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(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	**DOSAGE AND ADMINISTRATION**
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

– 5% Dextrose Injection, USP
– Lactated Ringers Injection, USP
– Lactated Ringers and 5% Dextrose Injection
– 5% Dextrose and 0.45% Sodium Chloride Injection, USP
– 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Rev. X 06/90

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ANESTH ANALG 125
1990;71:125–9

Effect of Dexmedetomidine, a Selective and Potent α_2-Agonist, on Cerebral Blood Flow and Oxygen Consumption During Halothane Anesthesia in Dogs

Bente R. Karlsson, MD, Marianne Forsman, MD, Ole K. Roald, MD, Mona S. Heier, MD, and Petter A. Steen, MD, PhD

KARLSSON BR, FORSMAN M, ROALD OK, HEIER MS, STEEN PA. Effect of dexmedetomidine, a selective and potent α_2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 1990;71:125–9.

The effect of the α_2-agonist dexmedetomidine on the cerebral blood flow (CBF) and the metabolic rate for oxygen was studied by a sagittal sinus outflow technique in dogs during halothane anesthesia. Dexmedetomidine was given in a dose (10 μg/kg) reported to reduce the anesthetic requirement of halothane by 90%. During 0.9% halothane anesthesia dexmedetomidine caused a significant reduction in CBF without influencing the metabolic rate for oxygen. Reducing the halothane concentration to 0.1% caused no further change in CBF, but increased the metabolic rate for oxygen 19%. The cerebral vasoconstrictive effect, combined with the 90% reduction in MAC for halothane, indicates that dexmedetomidine might be a useful adjunct to inhalation anesthetics during neurosurgery in situations where an increase in CBF should be avoided.

Key Words: BRAIN, CEREBRAL BLOOD FLOW AND METABOLISM—dexmedetomidine effect. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY, dexmedetomidine.

Dexmedetomidine, a new selective and potent centrally acting α_2-agonist, significantly reduces the dose requirement of inhalational anesthesia (1–3) probably through inhibition of central noradrenaline release (4–6). In experimental animals the minimum alveolar concentration (MAC) for halothane and isoflurane is reduced by more than 90% by dexmedetomidine in doses that are hemodynamically well-tolerated (1,3). In fact, data indicate that the drug itself might be a potent anesthetic (7,8).

In neuroanesthesia it is important to know the effect of any drug or combination of drugs used on cerebral blood flow (CBF) and energy consumption. Cerebral vasodilation can lead to a raised intracranial pressure, which may be deleterious in situations such as head injury or intracranial hemorrhage; an impaired CBF-to-energy consumption ratio might be deleterious when the blood supply is already marginal. Inhalation anesthetics are frequently used in neuroanesthesia. We have investigated the effect of dexmedetomidine on CBF and cerebral energy consumption (cerebral metabolic rate for oxygen, $CMRo_2$) during halothane anesthesia in dogs. Cerebral blood flow was measured by a sagittal sinus outflow technique. This is the only model that allows both on-line continuous measurement of CBF and the arteriovenous oxygen differences from the same area, and it is the model in which the effects of anesthetic agents on CBF and $CMRo_2$ have been most systematically examined (9).

Methods

The protocol of this study was approved by The National Animal Investigation Committee. Six unmedicated, fasting beagle dogs of either sex, weighing 10–16 kg, were studied. Anesthesia was induced and maintained during the surgical procedure with halothane at an end-expiratory concentration of 0.9% in 60%–70% nitrous oxide and oxygen. Succinylcho-

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Table 1. Arterial Blood Gas Values in Six Dogs During 0.9% Halothane Anesthesia Before (H 0.9%) and After (H 0.9% + D) an Infusion of 10 μg/kg Dexmedetomidine, and After a Reduction in Halothane Concentration to 0.1% (H 0.1% + D)

	pH	Pco_2	Po_2	BB
H 0.9%	7.31	5.1	20.5	41.4
	(7.29–7.33)	(4.9–5.3)	(18.5–21.8)	(40.4–41.5)
H 0.9% + D	7.31	5.1	19.9	41.0
	(7.30–7.32)	(4.9–5.6)	(18.2–21.9)	(40.4–43.1)
H 0.1% + D	7.34[a]	4.9[a]	21.0[a]	42.2
	(7.33–7.37)	(4.3–5.0)	(19.3–22.6)	(41.2–42.9)

BB, buffer base.
Medians and 95% confidence intervals are given.
[a] $P < 0.05$ vs H 0.9% and H 0.9% + D.

line (2 mg/kg) was given intravenously to facilitate endotracheal intubation, and thereafter continuously infused at a rate of 7.5 mg·kg^{-1}·h^{-1} to maintain muscle paralysis. Ventilation was controlled with a Harvard pump. End-expiratory concentration of CO_2, halothane, and nitrous oxide was continuously monitored (Capnomac, Datex, Instrumentarium Corp., Helsinki, Finland), and the ventilation adjusted to maintain a constant end-tidal CO_2 concentration close to 5.0%. Sodium bicarbonate was administered when necessary to keep the buffer base close to 42 mmol/L.

Cannulae were inserted into the femoral artery for blood sampling and continuous monitoring of the mean arterial blood pressure (MAP), and into the femoral vein for fluid and drug administration. The electrocardiogram was recorded from two upper limb leads. Body temperature was measured with a rectal thermometer, and brain temperature with a nylon isolated copper/constantan thermoelectric sensor placed epidurally. Both temperatures were maintained near 37°C with heating pads and lamps. A four-lead bifrontoparietal electroencephalogram (EEG) was recorded from needle electrodes inserted in the periostal tissue over the frontal and parietal cranial regions. Bilateral bipolar longitudinal derivations at a calibration of 150 μV/cm and paper speed of 30 mm/s were obtained.

After heparinization (20,000 IU intravenously) the sagittal sinus was exposed, isolated, and cannulated as previously described (10,11) for direct measurement of CBF from anterior, superior, and lateral portions of both hemispheres (equal to approximately 54% of total brain weight). The blood from the sagittal sinus was passively transported through a 25-cm extracorporeal loop into the left external jugular vein, which was cannulated with the Seldinger technique. Sagittal sinus blood flow was continuously recorded as it passed through an electromagnetic flowprobe (Nycotron 376, Drammen, Norway) in this loop. The calibration was frequently checked by direct measurements of timed collections of blood.

Arterial and sagittal sinus blood gases were determined by electrodes at 37°C (AVL 945, Graz, Austria). The oxygen saturation of hemoglobin was measured by a spectrophotometric method (12,13). Blood oxygen contents were calculated using 1.34 mL/g as the oxygen carrying capacity of hemoglobin, and using $CMRo_2$ as the product of CBF and the arterial to sagittal sinus blood oxygen content difference.

When the surgical procedure was completed, nitrogen was substituted for nitrous oxide while the end-expiratory halothane concentration was kept at 0.9%. After a stabilization period of at least 15 min, all variables were measured in duplicate, and $CMRo_2$ was calculated (H 0.9%). Thereafter 10 μg/kg dexmedetomidine (Farmos Group Ltd., Turku, Finland) was given as a continuous infusion over 15 min, and 10 min after its completion a new set of measurements were obtained (H 0.9% + D). End-expiratory halothane was then reduced to 0.1% over a period of 20 min, and kept at this concentration for 5 min before the last set of variables were measured (H 0.1% + D).

At the end of the experiment the animal was killed by an intravenous injection of KCl, and the brain was removed and weighed.

Results are given as medians and their 95% confidence intervals. The Friedman nonparametric statistical analysis was applied for evaluation of the results. Differences were considered significant when $P < 0.05$.

Results

A small but significant increase in arterial pH and Po_2 as well as a decline in median Pco_2 from 5.1 to 4.9 kPa was seen by the end of the experiments (Table 1). The median heart rate significantly decreased from 105 to 84 beats/min after the infusion of dexmedetomidine, with a further decline to 67 beats/min when the halothane concentration was reduced to 0.1% (Table 2). There were no significant differences in hemoglobin concentration, MAP, and rectal or epidural temperature during the experiments.

Cerebral blood flow was 88 mL·100 g^{-1}·min^{-1} (range 73–99) with halothane at an end-expiratory concentration of 0.9% (Figure 1), and declined significantly to 58 mL·100 g^{-1}·min^{-1} (range 42–65) after dexmedetomidine had been given. No further change in CBF occurred when the halothane concentration was reduced to 0.1%.

Table 2. Physiologic Variables in Six Dogs During 0.9% Halothane Anesthesia Before (H 0.9%) and After (H 0.9% + D) an Infusion of 10 μg/kg Dexmedetomidine, and After a Reduction in Halothane Concentration to 0.1% (H 0.1% + D)

	Hb	MAP	HR	Tp rect	Tp epid
H 0.9%	13.4	83	105	37.0	37.0
	(11.7–14.4)	(70–99)	(85–112)	(36.9–37.3)	(37.0–37.0)
H 0.9% + D	13.3	90	84[a]	37.1	37.0
	(12.2–14.9)	(85–95)	(72–90)	(37.0–37.6)	(37.0–37.0)
H 0.1% + D	13.3	90	67[b]	37.0	37.0
	(11.8–14.2)	(71–104)	(52–76)	(36.6–37.2)	(36.7–37.0)

Hb, hemoglobin; MAP, mean arterial pressure; HR, heart rate; Tp rect, rectal temperature; Tp epid, epidural temperature.

Medians and 95% confidence intervals are given.

[a] $P < 0.05$ vs H 0.9%.

[b] $P < 0.05$ vs H 0.9% + D and H 0.1% + D.

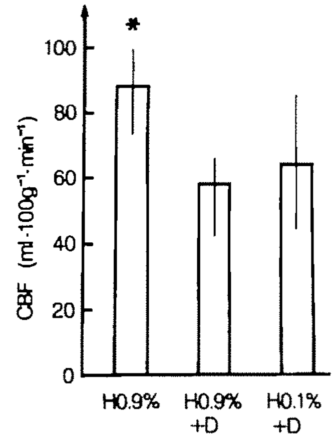

Figure 1. Cerebral blood flow in dogs during anesthesia with 0.9% halothane before (H 0.9%) and after (H 0.9% + D) an infusion of 10 μg/kg dexmedetomidine, and after a reduction in halothane concentration to 0.1% (H 0.1% + D). Medians and 95% confidence intervals are given. $n = 6$. *$P < 0.05$ vs H 0.9% + D and H 0.1% + D.

The cerebral metabolic rate for oxygen was 3.8 mL·100 g^{-1}·min^{-1} (range 2.8–4.7) with 0.9% halothane (Figure 2). Dexmedetomidine infusion did not significantly affect the oxygen consumption rate, but when the halothane concentration was reduced to 0.1% in the presence of the drug, CMRo$_2$ increased to 4.4 mL·100 g^{-1}·min^{-1} (range 3.9–4.7).

During anesthesia with 0.9% halothane the EEG showed a pattern of dominant 15–20 s^{-1} activity with a mean amplitude of 60 μV (Figure 3). Immediately following the dexmedetomidine infusion a slight increase of amplitude in the dominant fast activity accompanied by an additional slower 3–5 s^{-1} activity of moderate amplitude was seen. When the halothane concentration was reduced to 0.1%, the fast activity was markedly reduced in amplitude and the slower potentials disappeared in four of six dogs.

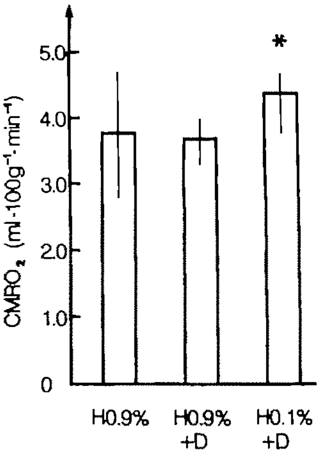

Figure 2. Cerebral metabolic rate of oxygen in dogs during anesthesia with 0.9% halothane before (H 0.9%) and after (H 0.9% + D) an infusion of 10 μg/kg dexmedetomidine, and after a reduction in halothane concentration to 0.1% (H 0.1% + D). Medians and 95% confidence intervals are given. $n = 6$. *$P < 0.05$ vs H 0.9% and H 0.9% + D.

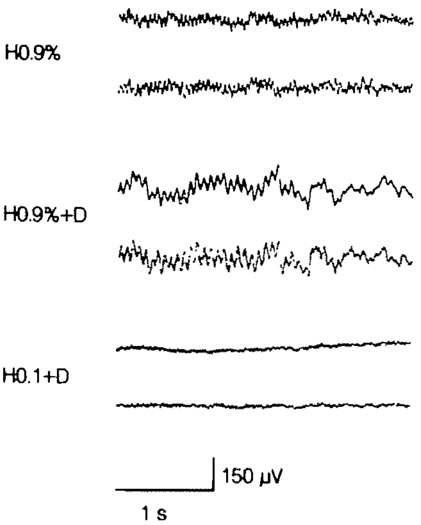

Figure 3. A representative bifrontoparietal EEG recording during 0.9% halothane anesthesia before (H 0.9%) and after (H 0.9% + D) an infusion of 10 μg/kg dexmedetomidine, and after a reduction in halothane concentration to 0.1% (H 0.1% + D).

Discussion

Dexmedetomidine is a highly selective and potent centrally acting α_2-agonist inhibiting the release of noradrenaline (4,14). Central noradrenergic neurotransmission has been linked to the dose requirement for anesthesia. Thus, manipulations that decrease central noradrenaline release also reduce the anesthetic requirement during surgical stimulation as reflected by a lower MAC value (5,6). Not surprisingly therefore, several investigations have proven dexmedetomidine to be a potent anesthetic sparing agent with prominent analgetic and hypnotic effects of its own (1–3,7,8). In experimental animals, MAC for halothane and isoflurane is reduced in a dose-dependent way by dexmedetomidine (1,2). Dexmedetomidine (10 μg/kg) reduced the MAC for halothane in dogs from 0.9% to 0.1% (1). We therefore chose to evaluate the effects of dexmedetomidine on CBF and $CMRo_2$ during halothane anesthesia at these two concentrations. The same authors (1) also observed a dose-dependent decrease in heart rate without a change in MAP after dexmedetomidine administration, similar to what we found in the present study.

The CBF values observed in this study during 0.9% halothane anesthesia correspond well with the findings of others using the same model (15). Dexmedetomidine caused a significant reduction in CBF during continuous 0.9% halothane anesthesia. It has previously been shown that 20 μg/kg dexmedetomidine increases systemic vascular resistance by 350% in dogs (3). Other investigators have reported only a tendency (nonsignificant) toward increasing systemic vascular resistance after 10 μg/kg dexmedetomidine despite a reduction in cardiac output from approximately 2.5 to 1 L/min without a fall in MAP (1). The present results indicate that dexmedetomidine is a cerebral vasoconstrictor in the presence of 0.9% halothane.

Halothane is a cerebral vasodilator (16), and whether dexmedetomidine has a cerebral vasoconstrictive effect in itself or only cancels the vasodilating effect of halothane could not be determined. The latter may be the case as the 30% reduction in CBF with dexmedetomidine equals that reported by others (15) for a reduction in halothane from 0.9% to 0.1%, and the same reduction in halothane concentration caused no further decrease in CBF in the present study.

The plasma half-life of dexmedetomidine in dogs is approximately 1 h (17), and although all measurements in our study were undertaken within that period, it cannot be excluded that a cerebral vasoconstrictive effect of dexmedetomidine was wearing off, thereby canceling an expected reduction in CBF with the reduction in halothane concentration from 0.9% to 0.1%. Randomizing the order of measurements might possibly have answered this question, but then the interpretation of the EEG changes after the dexmedetomidine infusion would have been difficult. Besides, some of the experiments would have taken longer as halothane could not be reduced to 0.1% before dexmedetomidine was given if anesthesia was to be maintained. Neither methods for plasma concentration analysis of dexmedetomidine nor pharmacokinetic data on a continuous infusion of the drug were available to us. Considering the half-life of dexmedetomidine, we therefore chose not to randomize the order of measurements.

A cerebral vasoconstrictive effect of dexmedetomidine is consistent with the results of former investigations with clonidine, a less specific and potent α_2-agonist. Clonidine has been shown to decrease CBF both in healthy human volunteers and in pentobarbital-anesthetized cats (18,19). In the latter study the CBF response to hypercarbia was reduced as well.

During anesthesia with 1 MAC halothane no change in energy consumption was seen after dexmedetomidine infusion. The 19% increase in $CMRo_2$ seen when the halothane concentration was reduced from 0.9% to 0.1% corresponds well with the 17% (15) and the 23% (20) change in $CMRo_2$ previously reported in dogs. Thus the increase in $CMRo_2$ seen in this study is most likely due to the reduced concentration of halothane.

Succinylcholine was used for muscle relaxation in this study. A bolus injection of succinylcholine has been shown to increase CBF transiently in this model, but not $CMRo_2$ (21). During 3–4 h of 1 MAC isoflurane anesthesia and a continuous infusion of succinylcholine in the same model, CBF and $CMRo_2$ were completely stable (11). Thus it seems unlikely that the use of succinylcholine infusion in our study could have seriously affected the results.

Dexmedetomidine seemed to accentuate the halothane-induced changes in the EEG, as both the amplitude of the dominant 15–20 s^{-1} rhythm and the slow wave/high amplitude activity seen with 0.9% halothane increased after infusion of the drug. When halothane was reduced to 0.1%, the amplitude of the dominant rhythm decreased to a slightly lower level than would have been expected with this concentration of halothane alone. Thus dexmedetomidine itself might cause a slightly reduced amplitude when compared with normal EEG activity, but the changes seem to be small.

In conclusion dexmedetomidine did not appear to affect $CMRo_2$ but was a cerebral vasoconstrictor, at least in the presence of 0.9% halothane in the dog. Thus the drug might be a suitable background anesthetic when studying the $CMRo_2$ effects of other drugs in animals. The cerebral vasoconstrictive effect, combined with a 90% reduction in MAC for halothane, could make dexmedetomidine a possible useful adjunct to halothane, especially during neurosurgery. The present data cannot necessarily be extrapolated to other species as species differences in distribution of α-adrenergic receptor subtypes in the brain have been reported (22). The cerebral arteries from dogs seem to respond more to α_2-stimulation in vitro than arteries from monkeys, but to our knowledge no human data are available.

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Postoperative Pain Control With a Continuous Infusion of Epidural Sufentanil in the Intensive Care Unit: A Comparison With Epidural Morphine

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DYER RA, ANDERSON BJ, MICHELL WL, HALL JM. Postoperative pain control with a continuous infusion of epidural sufentanil in the intensive care unit: a comparison with epidural morphine. Anesth Analg 1990; 71:130–6.

A prospective, randomized, double-blind trial was conducted to compare the analgesic actions and side effects of sufentanil continuously infused (5 μg/h) into the lumbar epidural space (L2-3) with those of an infusion of lumbar epidural morphine (0.5 mg/h). Forty patients admitted to an intensive care unit after elective major abdominal surgery participated over a varying period of 24–40 h. Postoperative pain was treated with an epidural bolus of either sufentanil (50 μg) or morphine (5 mg), followed by a continuous infusion of the same opiate. The quality of pain relief was similar in each group. The sufentanil group had a more rapid onset of analgesia. The incidence of nausea and vomiting, pruritus, and drowsiness was similar in the two groups. In spontaneously breathing patients there were no respiratory complications requiring treatment. Forced vital capacities were statistically significantly better during the first 1–4 h with sufentanil.

Key Words: ANALGESICS, SUFENTANIL. ANESTHETIC TECHNIQUES, REGIONAL, EPIDURAL.

Continuous low dose morphine (0.1–0.5 mg/h) delivered epidurally is an established method of postoperative analgesia after thoracic and abdominal surgery (1,2). There is no difference in the quality of pain relief between epidural and intramuscular morphine administration, but the duration of analgesia is longer and achieved by smaller doses given epidurally (3). However, side effects of epidural morphine include urinary retention, nausea, vomiting, and occasional hypotension. Fentanyl, a shorter-acting opiate, has been shown to be effective by continuous epidural infusion over a 24-h period after upper abdominal surgery, with fewer side effects (4).

Sufentanil is a fentanyl derivative with properties that may render it even more suitable than morphine for continuous epidural techniques. It is 5–7 times more potent than fentanyl and has a short half-life ($T_{1/2\,\alpha}$, 1.4 min; $T_{1/2\,\beta}$, 17.1 min). Sufentanil is highly lipid-soluble, with high receptor affinity, suggesting a rapid onset of intense analgesia with a longer duration (5,6). Sufentanil is marketed as a sterile preservative-free aqueous solution, minimizing the danger of neurogenic toxicity. The aim of this study was thus to compare in a randomized, prospective, double-blind trial the analgesic actions and side effects of sufentanil and morphine administered as continuous infusions into the lumbar epidural space in critically ill patients in an intensive care unit.

Methods

Forty patients admitted for postoperative care in our surgical intensive care unit (SICU) after elective major upper abdominal surgery were studied. Patients were referred on the basis of preexisting cardiopulmonary disease or the extent of the surgical procedure. There were 23 major vascular cases. The study was approved by the University of Cape Town Ethics Committee and informed written consent was obtained. Preoperatively, instructions were given regarding interpretation of the numerical pain score,

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and the patient was familiarized with a Wright respirometer. The trial was double-blind. Random allocation of patients into two groups was made in the pharmacy, where the sterile, preservative-free opiate solutions were prepared. Group 1 received morphine, and group 2 received sufentanil. There were 20 patients in each group. Anesthetic technique included a benzodiazepine premedication for balanced general anesthesia, the only restriction being a limitation on intraoperative opiates to fentanyl $< 3\ \mu g \cdot kg^{-1} \cdot h^{-1}$. No other opiates were used. Muscle relaxation was reversed in the operating room. Postoperatively an epidural catheter was inserted by one of the investigators at the L2-3 level, using the loss of resistance technique, and no further confirmation of placement was performed.

As soon as patients complained of pain, either verbally or employing the numerical pain scale, a bolus dose of epidural narcotic was given and an epidural narcotic infusion started after all baseline recordings had been made. Patients in group 1 were given a 5 mg in 10 mL saline bolus of morphine followed by infusion of 0.5 mg/h (20 mg/200 mL); those in group 2 received a 50 μg in 10 mL normal saline bolus of sufentanil and then an infusion of 5 μg/h (200 μg/200 mL normal saline). If additional analgesia was required, the attending nurse was free to administer 2–4 mg morphine intravenously as necessary. Surgical intensive care unit nurses were trained in the method of pain assessment and supervised by the investigators.

Determination of the patient's pain was made by:

1. Nurse assessment of response to stimuli such as coughing, movement, suctioning, or physiotherapy (severe pain 4, moderate 3, mild 2, no pain 1)
2. Patient assessment using a numerical pain score with anchor words (worst pain imaginable 10, to no pain 0)
3. Intravenous morphine supplementation required
4. Serial forced vital capacities (FVCs) performed in the semirecumbent position. The highest of three recordings made on each occasion was noted.

These measurements were made immediately before initial epidural opiate administration and then hourly over the period of study. At night this interval was extended if the patient was asleep.

Respiratory rate was monitored by the nurse assigned to the patient. Blood gas tensions were measured before epidural opiate administration and, thereafter, hourly for 2 h, then every 2 h for 4 h, and thereafter every 6 h, unless otherwise clinically indicated. Side effects were recorded objectively by the nurse, or if volunteered, by the patients. Pruritus and nausea and vomiting were simply noted as present or absent; sedation was recorded on a scale every hour ranging from calm and orientated to normal sleep, drowsy, or unrousable. Sedation was recorded as a side effect if a patient was classified as drowsy on this scale. A peripheral neurologic examination was made every day to check sensory and motor function.

Blood samples for measurement of serum sufentanil levels were withdrawn from the arterial line 5 min (seven patients) and 1, 6, 12, and 24 h (20 patients) after the first epidural injection. Samples were centrifuged and the supernatant stored at −20°C. Levels were subsequently measured in samples from patients in group 2 after the randomization code was cracked. A radioimmunoassay method was employed by Janssen Pharmaceutica. The assay sensitivity was 0.02 ng/mL (7).

Statistical analysis, in the form of a cross-sectional study at each hour, employed the Mann–Whitney U-test to compare patient pain scores, nurse pain scores, and FVCs between each group.

The χ^2-test was used to compare side effects and intravenous morphine supplementation between the two groups. Where the numbers were too small, the Fisher's exact probability test was used.

The Spearman rank correlation coefficient was used to determine the strength of association between the patient pain score and the nurse pain score.

The running median is a nonlinear smoother, which was used to attempt to demonstrate a trend of the scatterplot of Pa_{CO_2} over time. The median value for each of the consecutive subsets of Pa_{CO_2} values, conditional on the time of observation, was calculated (8).

A P level of ≤ 0.05 was considered significant throughout the study.

Results

The mean age of group 1 patients was 56.5 yr (range, 32–72 yr), weight 67.8 kg (range, 45–93 kg), and height 170.5 cm (range, 160–190 cm); corresponding figures for group 2 were 56.2 yr (range, 26–78 yr), 66.4 kg (range, 50–93 kg), and 166.8 cm (range, 155–180 cm). The two groups were comparable for age, weight, and height.

Mean pain scores for the two groups at each assessment time during the 40-h postoperative period are shown in Figure 1. Both groups complained of severe pain in the immediate postoperative period, pain scores being 8.85 in group 1 and 9.15 in group 2. Pain relief with sufentanil was rapid; the mean pain score in the sufentanil group was <5 in 1 h and <4 in

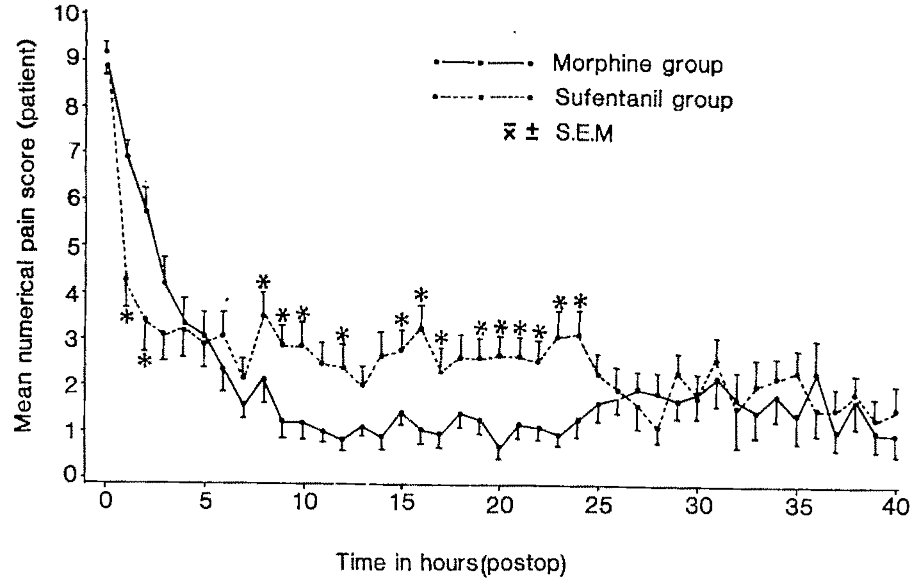


Figure 1. Comparison of patient pain scores in each group for the first 40 h after commencement of epidural administration of opiate. $^*P < 0.05$.

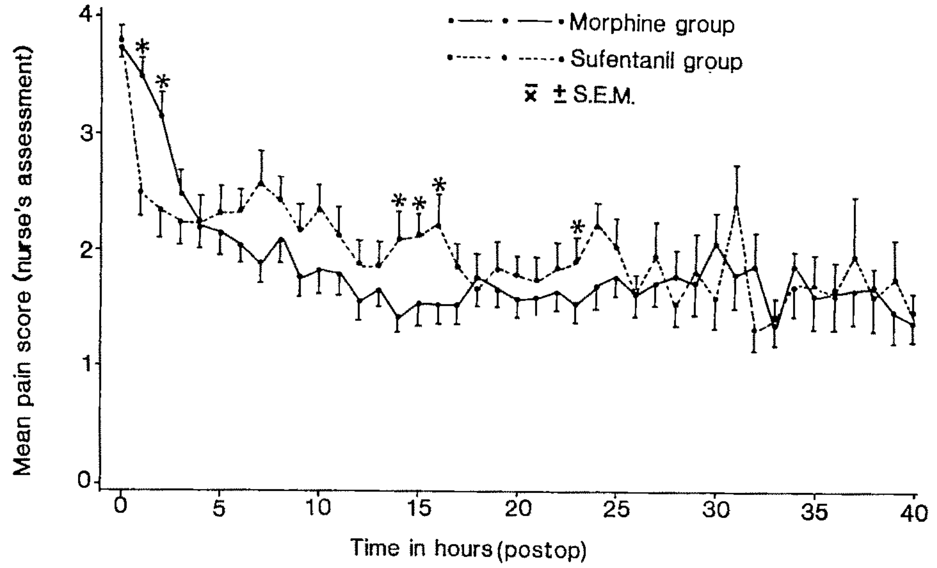


Figure 2. Comparison of mean nursing staff pain assessment in each group for the first 40 h after commencement of epidural opiate. $^*P < 0.05$. Key: 1 = none; 2 = mild; 3 = moderate; 4 = severe pain.

2 h. The corresponding times for morphine were 3 and 4 h, respectively. The pain scores were statistically different at hours 1 and 2 ($P < 0.02$) and lower in the sufentanil group, indicating rapid onset. There was again a significant difference for all but four scores between hours 8 and 24, and values were higher in the sufentanil group ($P < 0.05$).

The corresponding nursing staff assessments of pain levels are indicated in Figure 2. There was a good positive correlation between patient and nurse pain scores from hours 1 to 6 in both groups. This correlation persisted from hours 7 to 40 in the morphine group only, possibly indicating that the patient numerical pain score was more sensitive than the nursing verbal response scale.

The intravenous morphine supplementation is indicated in Table 1. Although more patients in the morphine group required intravenous morphine in hours 0 to 6, this was not statistically significant. From hours 7 to 40 the sufentanil group required statistically significantly more boluses ($P < 0.033$).

Table 2 shows the incidence of side effects. There were no statistically significant differences with respect to pruritus, nausea and vomiting, or sedation. By 12 h most patients were alert, cooperative, and comfortable. No patients in either group were unrousable at any time. One patient in the sufentanil group had a brief period of hypotension (mean arterial pressure, 50 mm Hg) shortly after the bolus, which responded well to fluid administration. Uri-

Table 1. Supplementary Analgesia

Number of additional intravenous morphine injections	0–6 h[a]		7–40 h[a]	
	Morphine	Sufentanil	Morphine	Sufentanil
0	8	13	13	5
1	5	2	3	5
≥2	7	5	4	10

[a] Number of patients in each group requiring the indicated number of boluses in the specified time periods postoperatively.

Table 2. Side Effects[a]

	Pruritus	Nausea/ vomiting	Sedation	
			0–6 h	7–40 h
Morphine	5	7	7	3
Sufentanil	1	5	8	6

[a] Number of patients out of 20 in each group.

nary retention was not assessed, as most patients were catheterized during their intensive care stay. There were no mortalities.

Twenty-four patients were mechanically ventilated (12 in each group). Three in group 1 and one in group 2 were ventilated for less than 4 h, and the remainder were ventilated for 10–21 h. Two patients in the morphine group were ventilated for 37 and 40 h due to respiratory complications related to preexisting cardiorespiratory disease.

Analysis of the respiratory data showed no significant differences at any time between rate of respirations, pH, or Paco$_2$ in the two groups. Running median smoothed plots of Paco$_2$ are shown in each group in Figures 3 and 4. These are the Paco$_2$ values of all spontaneously breathing patients, i.e., the 16 who were extubated in the operating room (eight in each group) and the postextubation values of all other patients. The medians lie below 6 kPa. Two patients in the sufentanil group had a single reading of Paco$_2$ >7 kPa and one patient in the morphine group had six consecutive values >7 kPa (kPa × 7.502 = mm Hg). Only one patient in each group transiently had a breath rate of <10 per minute. However, Paco$_2$ values were normal.

Changes in FVC, expressed as a ratio of the preoperative value, for 15 h are shown in Figure 5. Immediately postoperatively, before the epidural bolus, there was a marked decrease in FVC when compared with preoperative levels. Forced vital capacity in the sufentanil group improved dramatically in the first 3 h. The *P* value for comparison between groups was <0.05 for hours 1 to 4; thereafter there was no significant difference. There was a trend toward increasing vital capacity as pain scores declined, but this did not achieve statistical significance.

Mean plasma sufentanil levels at 5 min (seven patients), 1 h, 6 h, 12 h, and 24 h (20 patients) were all below 0.1 ng/mL, except for the 5-min value of 0.107 ng/mL.

Discussion

This study, conducted specifically in major abdominal surgical cases requiring postoperative intensive care management, suggests that epidural sufentanil as a bolus followed by continuous infusion is as safe and effective a means of postoperative analgesia as epidural morphine.

The rapid onset of analgesia using a bolus of 50 μg epidural sufentanil is consistent with other series (9–11). For morphine, analgesia after 6 h is the same in lumbar as in thoracic epidurals, due to migration of epidural morphine to thoracic regions (12). We noted a 3-h delay in our morphine group.

Theoretically, the high lipid solubility of sufentanil may limit the spread of analgesia, so that for good quality of analgesia the epidural may have to be sited in the center of the dermatomal area to be rendered pain-free. Excellent analgesia has been achieved after upper abdominal surgery, using three dose volumes of sufentanil in different sites: 50 μg/10 mL at the midpoint of the dermatomal area and 50 μg/20 mL and 50 μg/10 mL at the lumbar level (11). Durations of effect were 9.9, 6.9, and 5.4 h, suggesting that smaller dose volumes at lower spinal levels result in less cephalad spread. The subjective assessment of pain by patient numerical score and objective method of nurse pain score suggested a similar quality of analgesia in the two groups in our study. Duration of analgesia after a 50-μg lumbar epidural sufentanil bolus is quoted at 4 and 5.4 h after upper abdominal surgery and 6.7 h after lower extremity orthopedic procedures (9,11,13). This tallies with our findings, where the slight recurrence of pain at 8 h extending to 24 h in the sufentanil group was almost certainly due to an inadequate infusion rate.

The marked decrease in FVC ratio immediately postoperatively is a result of many factors, including reduced functional residual capacity secondary to pain and muscle splinting. An increase from 35% to 55% of the preoperative values has been found after epidural narcotics (14). Our patients had lower values, but were almost invariably smokers, evidenced an element of chronic lung disease, and were older than those in the latter study (14). There was a trend

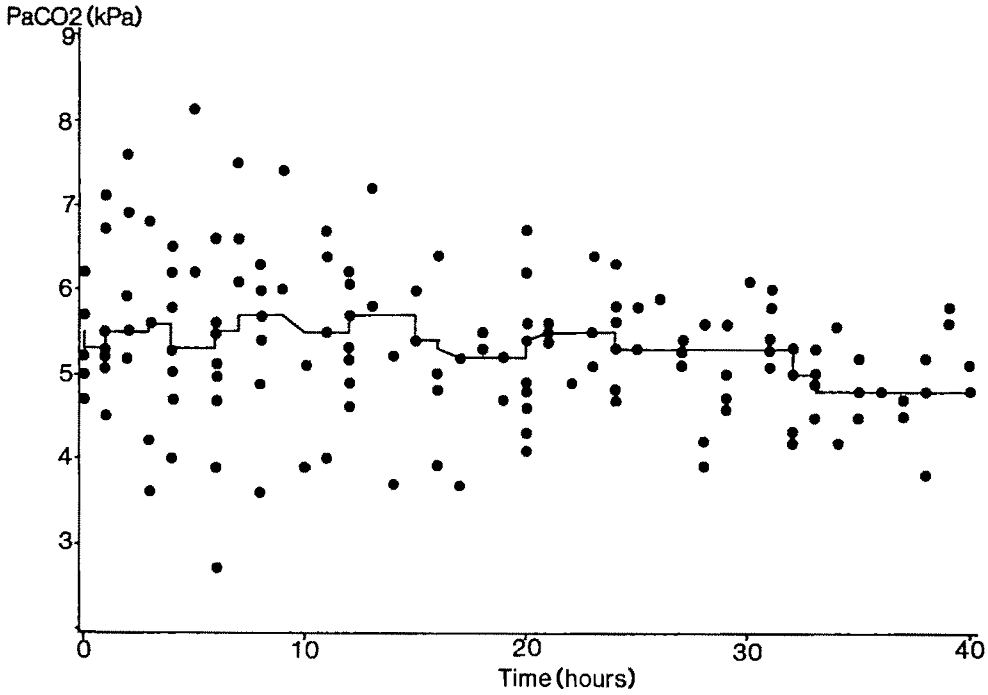
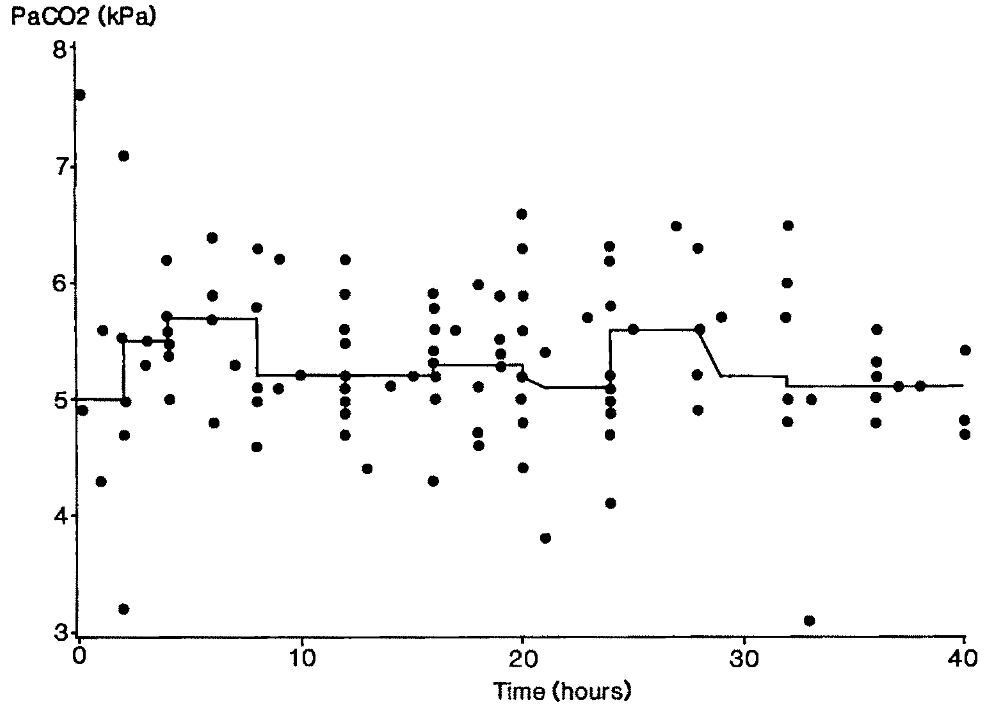


Figure 3. *Above*. Running median smoothed plot of Pa_{CO_2} values over time, of spontaneously breathing patients in the morphine group (kPa × 7.502 = mm Hg).

Figure 4. *Below*. Running median smoothed plot of Pa_{CO_2} values over time, of spontaneously breathing patients in the sufentanil group (kPa × 7.502 = mm Hg).

toward increasing FVC as pain scores declined. The sufentanil group had early rapid increases in FVC that plateaued, whereas the morphine group had a more gradual increase up to 4–6 h after initiation of the epidural opiate. Several studies have demonstrated the value of objective measures of respiratory function as an adjunct to pain assessment (13–15).



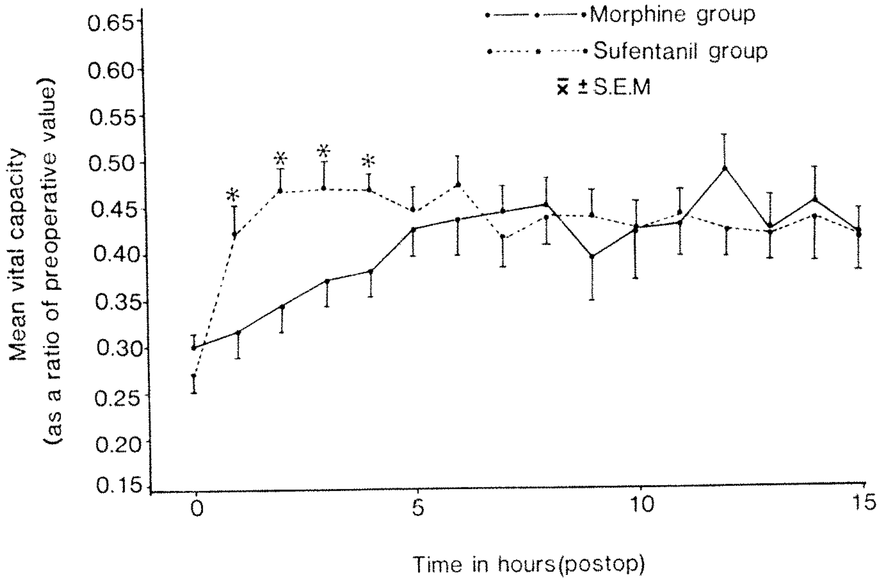


Figure 5. Comparison of changes in mean vital capacity in each group, expressed as a ratio of the preoperative value, for the 15 h after the commencement of opiate. $^*P < 0.05$.

Our results suggest that measurement of FVC ratio may be a useful objective pointer to improved pain relief, particularly in intubated patients, where there is a communication difficulty.

The amount of supplementary analgesia administered proved a weaker discriminator of effectiveness of analgesia between the two groups.

Sufentanil, with its high lipid solubility, may migrate less in cerebrospinal fluid and thus exhibit diminished cephalad spread, and may cause fewer cases of delayed respiratory depression (in 0.25%–0.40% of cases after epidural morphine) (16). Although there have been no reported cases of delayed respiratory depression after epidural sufentanil, the quoted incidence of early respiratory depression varies. Moderate decreases in respiratory rate and increases in arterial carbon dioxide tension in the first hour after epidural injection of sufentanil (15–75 μg) have been noted in 20 patients (9). It was concluded that respiratory depression was not evident. However, another study recorded that three of seven patients given 75 μg of lumbar epidural sufentanil developed severe respiratory depression within 30 min (10). In our study respiratory depression was assessed in all spontaneously breathing patients. No patients required treatment for respiratory inadequacy, and there were no cases of delayed respiratory depression.

Sedation is a well-known side effect of epidural sufentanil (9,13). The insignificant difference between the two groups with respect to this feature is noteworthy. Furthermore, no patients were unrousable, and sedation did not appear to delay weaning from mechanical ventilation or complicate either nursing procedure or pulmonary physiotherapy.

Although plasma levels of analgesics correlate poorly with quality of analgesia (17), it is noteworthy that all the sufentanil plasma levels in our patients were considerably lower than the values of 0.2–0.4 ng/mL after an intravenous bolus of 30 μg of sufentanil reported by others (18). This suggests, but does not prove, a spinal action in our cases.

Previously, an epidural infusion rate of 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of sufentanil has been employed following a maximal bolus of 0.6 μg/kg after abdominal surgery in nine patients, where anesthetic technique involved epidural bupivacaine, but no opiates (19). There was a tendency to systemic accumulation in this series. Using an infusion rate of 5 μg/h, we demonstrated no accumulation and minimal respiratory side effects; this rate could be safely increased for more ideal analgesia, but an increasing incidence of other side effects might occur. However, although effective as a postoperative analgesic technique, we do not recommend the use of continuous epidural sufentanil in an ordinary ward.

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Sedative and Hypnotic Midazolam-Morphine Interactions in Rats

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KISSIN I, BROWN PT, BRADLEY EL, Jr. Sedative and hypnotic midazolam-morphine interactions in rats. Anesth Analg 1990;71:137–43.

The midazolam-morphine interactions in relation to the sedative effect and in relation to the hypnotic effect were studied in rats. Two series of experiments (sedative and hypnotic) were performed. In the sedative series, doses that inhibited locomotor activity to 10% or more of the control level were determined when the agents were given singly or in combination. Dose-response curves were determined with a probit procedure. The ED_{50} values of both agents and their combination were compared with algebraic (fractional) and isobolographic analyses in one subseries of experiments. The effect of a small fixed dose of morphine (1/10 of ED_{50} value for the sedative effect) on the slope of the sedative dose-response curve for midazolam was determined in the other subseries. In the hypnotic series of experiments, doses (ED_{50}) that blocked the righting reflex with drugs given separately and in combination were determined by a probit procedure and, as in the sedative series, compared with algebraic (fractional) and isobolographic analyses.

Sedative interaction between midazolam and morphine was found to have a tendency for synergism (interaction coefficient of 1.56, $P > 0.05$) with decreased individual variability in the sedative response to the combination. Hypnotic midazolam-morphine interaction was highly synergistic with the interaction coefficient of 3.70 ($P < 0.0001$). A difference in the outcomes of midazolam-morphine interaction regarding sedation and hypnosis suggests that underlying mechanisms for these two effects are different; therefore, they should not be regarded as only increasing depths of the same action.

Key Words: ANALGESICS, MORPHINE. HYPNOTICS, BENZODIAZEPINES—midazolam. INTERACTIONS (DRUG), MIDAZOLAM-MORPHINE.

Benzodiazepine-opioid interactions for induction of unconsciousness in patients were found to be synergistic (1,2). Experiments in rats also demonstrated that the hypnotic diazepam-morphine interaction (end point–loss of the righting reflex) is highly synergistic (3). However, when the midazolam-morphine interaction was studied in patients with regard to the sedative effect, instead of expected synergism, simple summation of the effects has been found (4). The sedative effect and the hypnotic effect are often regarded as only increasing depths of the same action (5). Different types of interactions between the same agents with regard to the two effects might be evidence for the difference in the mechanism of action underlying these effects. The aim of the present study was to determine the type of midazolam-morphine interaction for the sedative effect in comparison with that for the hypnotic effect, and also to assess individual variability in the sedative response to the combination.

Methods

Experiments were performed on male Sprague–Dawley rats weighing 225–275 g. The protocol for this study was approved by the Institutional Panel on Laboratory Animal Care. Two series of experiments were performed: one with sedative and another with hypnotic interaction. As an index for the sedative effect we used the reduction of spontaneous locomotor activity; as an index for hypnotic effect, the loss of the righting reflex.

Spontaneous locomotor activity was measured with use of an Activity Meter (Opto-Varimex-Mini, Columbus Instruments, Columbus, Ohio) that counted the number of infrared beam interruptions (15 beams with sensors equally spaced [2.65 cm]) in the cage at a distance of 5.25 cm from the floor. Only ambulatory activity was taken into account, stereotypic movements that caused rapid and repeated interruptions of the same beam (e.g., grooming,

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digging, scratching) were not considered. Each rat was placed into the activity cage alone and only once for 30 min. Locomotor activity was measured during the 15–30-min interval; the 0–15-min interval was omitted to exclude exploration associated with new surroundings (activity cage). The 30-min limit for locomotor activity measurements was chosen on the basis of the report by Oka and Hosoya (6) on the dose-dependent inhibitory effect of morphine on locomotor activity in rats within this time interval. Locomotor activity during this interval in control rats (intramuscular injection of saline 15 min before the test) was 289 ± 124 (mean ± SD, $n = 10$). Because one of the aims of this study was to compare the sedative interaction with hypnotic interaction that has quantal nature (all or none for loss of the righting reflex), we also used a quantal end point for the sedative effect: suppression of locomotor activity to 10% of that in the control group. Activity of 29 beam crossings or less was considered as a positive response to a drug or the drug combination, which allowed us to obtain a quantal curve of a graded type of response. All testing was done in a quiet room between 8 AM and 1 PM. Each animal was given, intramuscularly, one predetermined dose of midazolam hydrochloride (Hoffman-LaRoche), morphine sulfate (Lilly), or their combination. Times between injections and the test were based on the times to peak effects: 30 min for morphine, 15 min for midazolam. The peak times were chosen after preliminary experiments. In the combined drug experiments, each drug was injected separately to synchronize the occurrence of the peak effects.

Two subseries of experiments for sedative interaction were performed. In one subseries, the diazepam-morphine interaction was analyzed on the basis of comparison of the ED_{50} values of the drugs given separately and in combination. In another subseries, the effect of a fixed dose of morphine on the slope of the midazolam dose-response was studied. In the first subseries, the interaction was determined in two steps. Dose-response curves were obtained first, and ED_{50} values were calculated. Then, algebraic (fractional) (7) and isobolographic (8) analyses were used to characterize the type of interaction. Three dose-response curves (three groups of experiments) were determined: two with midazolam and morphine given alone and a third with a morphine-midazolam combination. Five subgroups of four animals were used to determine the curve in each group of experiments, with doses equally spread to give a range that reaches the end point in none or all of the animals in a subgroup. The doses of morphine and midazolam used in this subseries to determine sedation are presented in Table 1 (part 1, A, B, C). In the combined group (C) the midazolam-morphine weight ratio was 1:6. This ratio was based on the data obtained in preliminary experiments on the relative sedative potencies of midazolam and morphine. We maintained the midazolam-morphine ratio at approximately equipotent levels. The doses of both components of the combination rose by steps from one subgroup of rats to another with a constant weight ratio between the components of 1:6.

The construction of the dose-response curves and determination of ED_{50} values were based on the probit procedure (9). ED_{50} values from all three subgroups of experiments were used for algebraic (fractional) analysis (7). The doses of the midazolam and morphine components of the combination (Ac and Bc) were expressed as fractions of the doses of these drugs that produce the same effect when given separately (Ac/As and Bc/Bs). The sum of the fractional doses equals 1.0 in summation, as expressed by the following equation:

$$\frac{Ac}{As} + \frac{Bc}{Bs} = 1.0.$$

In synergism, the sum of fractional doses is <1.0, and in antagonism, it is >1.0.

With isobolographic analysis (8), single-drug ED_{50} points were placed on the dose coordinates of the isobologram and a combined ED_{50} point in the dose-field (Figure 1). The deviation of a combined ED_{50} point from an additive line (straight line joining single-drug ED_{50} points) was measured as the length of a line running from the point in question to the additive line in a perpendicular manner. This distance was used to determine whether a statistically significant difference was present. The standard error of this distance was computed by the method of propagation of error (10). Error estimates from a combined ED_{50} point, as well as single-drug ED_{50} points, were used. An approximate t-test used to test the assumption of additivity was then obtained as the ratio of the measured distance to its standard error (11).

In the second subseries of experiments, the effect of a small dose of morphine (1/10 of the morphine ED_{50} value for the sedative effect) on the slope of the midazolam dose-response curve was studied. Because the slope of the dose-response curve reflects individual variability in sensitivity to the agent, the aim of this subseries was to determine whether morphine changes the variability in the sedative response to midazolam. In this subseries, two groups of experiments were performed: one with morphine and one with saline (control). Morphine was used in

Table 1. Doses of Midazolam and Morphine Used to Determine Sedative Interaction

				Dose (mg/kg)	
Subseries	Group	Subgroup	*n*	Midazolam	Morphine
1. Analysis of changes in ED_{50} values of dose-response curves	A. Midazolam	1	4	0.2	Saline
		2	4	0.5	Saline
		3	4	2.0	Saline
		4	4	5.0	Saline
		5	4	10.0	Saline
	B. Morphine	1	4	Saline	3.0
		2	4	Saline	4.0
		3	4	Saline	5.0
		4	4	Saline	7.0
		5	4	Saline	10.0
	C. Combination	1	4	0.15	0.9
		2	4	0.25	1.5
		3	4	0.35	2.1
		4	4	0.50	3.0
		5	4	0.75	4.5
2. Analysis of changes in slope of midazolam dose-response curve	A. Midazolam without morphine	1	8	0.2	Saline
		2	8	0.5	Saline
		3	8	2.0	Saline
		4	8	5.0	Saline
		5	8	10.0	Saline
	B. Midazolam with morphine	1	8	0.2	0.6
		2	8	0.5	0.6
		3	8	0.7	0.6
		4	8	1.0	0.6
		5	8	2.0	0.6

a fixed dose of 0.6 mg/kg, and the dosage of midazolam was varied to obtain the dose-response curve (Table 1, part 2, A,B). To show statistically significant changes in the slopes of dose-response curves, more animals are needed than with the changes in the ED_{50} values. Therefore, in this subseries we had eight animals in each subgroup. Morphine (or saline) was injected intramuscularly 30 min before the beginning of the test; midazolam was injected intramuscularly 15 min before the test's beginning.

To compare the midazolam-morphine interaction for the sedative effect with that for the hypnotic effect, the second series of experiments with the righting reflex as an end point was performed. The righting reflex was tested in the following way. The rat was placed into a cylindrical, revolving cage with its paws down. Then, the cage was rotated (one revolution per 15 s) to place the rat on its back. After this, the rotator was stopped for 15 s. If the rat could not be placed on its back for 15 s or could not remain on its back for an additional 15 s the righting reflex was considered not blocked. The experiments were conducted with the rats in a clear chamber, 30 × 25 × 40 cm, into which oxygen was delivered (4 L/min). The rat's hind leg (for injection into the saphenous

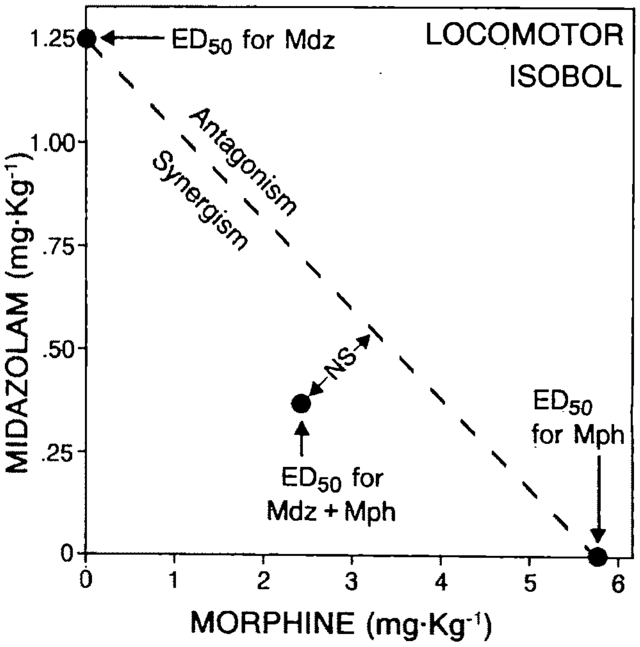

Figure 1. ED_{50} isobologram for the interaction of midazolam (Mdz) and morphine (Mph) as characterized by suppression of spontaneous locomotor activity. ED_{50} values generated by probit analysis indicate the dose that provides suppression of locomotor activity to 10% or more of the control level in 50% of animals. The *dashed straight line* is an additive line. NS indicates that the tendency for synergism did not reach statistical significance.

Table 2. Doses of Midazolam and Morphine Used to Determine Hypnotic Interaction

			Dose (mg/kg)	
Group	Subgroup	*n*	Midazolam	Morphine
A	1	4	6	Saline
	2	4	10	Saline
	3	4	15	Saline
	4	4	20	Saline
B	1	4	Saline	8
	2	4	Saline	10
	3	4	Saline	12
	4	4	Saline	15
C	1	4	0.5	0.7
	2	4	0.7	1.0
	3	4	1.0	1.5
	4	4	1.4	2.0
	5	4	2.1	3.0

vein) could be extended outside the chamber through a slot. The animals were placed in the chamber with oxygen at least 15 min before a first injection. Each animal was given one predetermined dose of morphine, midazolam, or the midazolam-morphine combination. Times between injections of drugs and the righting reflex test were based on the times to peak effect for these agents: 15 min for morphine and 3 min for midazolam. The peak times were chosen after preliminary experiments. In the combined drug experiments, each drug was injected separately to synchronize the occurrence of the peak effects. The analyses of drug interaction were performed as described for the first series of experiments. The drug doses used to determine loss of the righting reflex are presented in Table 2. Determination of the ED_{50} values and analysis of interaction duplicated that for the sedative series of experiments.

Results

Algebraic (fractional) analysis of the midazolam-morphine interaction for the sedative effect as characterized by suppression of locomotor activity is presented in Table 3. The midazolam ED_{50} value for this end point was 1.2 mg/kg (95% confidence limits, 0.4–3.6 mg/kg); the morphine ED_{50} value for this end point was 5.8 (3.6–9.4) mg/kg. The same level of sedation was reached when doses of midazolam and morphine given in combination were 0.4 and 2.1 mg/kg, respectively. When the doses of the combination components were presented as fractions of the ED_{50} values of midazolam and morphine given alone, the sum of fractions was 0.64. The ratio of the expected sum of fractional doses of the drugs if they are additive (i.e., 1.0) to the obtained sum of fractional doses (coefficient of interaction) was 1.56, indicating a tendency for synergism (that did not reach statistical significance). The isobolographic analysis (Figure 1) also demonstrated that midazolam-morphine sedative interaction was not significantly different from simple summation.

The effect of the fixed dose of morphine representing 1/10 of its sedative ED_{50} value on the midazolam dose-response curve for the sedative effect is presented in Figure 2. A statistically significant change was seen in the slope of the midazolam dose-response curve, which became steeper with the addition of morphine: a slope of 1.34 versus 3.96 with morphine ($P < 0.02$). However, morphine did not cause a significant shift of the midazolam dose-response curve to the left along the dose axis. The change in the position of the curve was related primarily to the upper part of the curve.

Algebraic (fractional) analysis of the midazolam-morphine hypnotic interaction as characterized by loss of the righting reflex is presented in Table 4. In combination, the observed sum of the fractional doses was significantly greater than unity (i.e., 1.00) which is expected in the case of the additive effect, and the coefficient of interaction was 3.70 ($P < 0.0001$), which was indicative of a profound synergism. The isobolographic analysis of the midazolam-morphine interaction also demonstrating synergism is shown in Figure 3.

Discussion

The results obtained in the present study with the midazolam-morphine sedative interaction demonstrated a tendency for synergism that failed to reach statistical significance. It was shown also that morphine, used in a small fixed dose, made the slope of the midazolam dose-response curve steeper, indicating a decrease in individual variability of sensitivity to the sedative effect of midazolam. Morphine changed the slope of the midazolam dose-response curve mainly by shifting the upper end of the curve to the left along the dose axis. This suggests that morphine contributed to the sedative effect only in animals that are least sensitive to midazolam. The fact that morphine contributed to the sedative effect of midazolam only to a limited extent agrees with the outcome of the study of the midazolam-morphine sedative interaction in patients, which demonstrated simple summation of the sedative effects of these two agents (4). The ability of alfentanil to shift the midazolam dose-

Table 3. Midazolam-Morphine Sedative Interaction

Group	Equieffective doses (ED_{50}) Fraction / mg/kg: Midazolam component	Morphine component	Sum of fractions	Coefficient of interaction[a]
A. Midazolam	$\frac{\mathbf{1.00}}{1.2(0.4,3.6)^b}$	**0.00**	**1.00**	—
B. Morphine	**0.00**	$\frac{\mathbf{1.00}}{5.8(3.6,9.4)}$	**1.00**	—
C. Combination	$\frac{\mathbf{0.28}}{0.4(0.2,0.8)}$	$\frac{\mathbf{0.36}}{2.1(1.0,4.7)}$	**0.64**	**1.56** NS

NS, not significant.

[a] Measure of interaction representing the ratio of the expected sum of fractions if the drugs are additive (i.e., 1.00) to the obtained sum of fractions.

[b] 95% confidence limits are in parentheses.

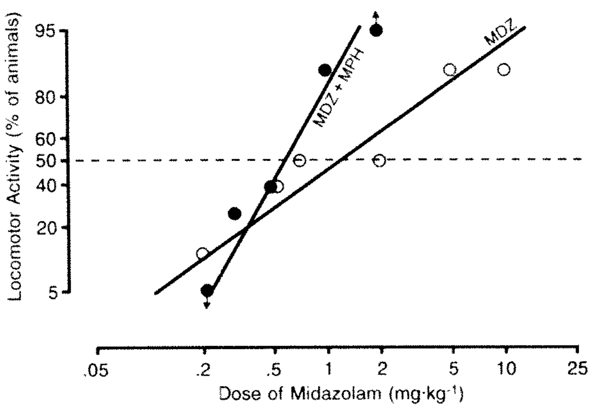

Figure 2. Sedative dose-response curves for midazolam (MDZ) with and without the addition of the fixed dose of morphine (MPH) (0.6 mg/kg, 1/10 of the morphine ED_{50} value for the same end point). *Vertical axis*—probit scale, *horizontal axis*—log scale. Each *dot* represents the incidence of suppression of locomotor activity to 10% of control level or more in a group of five animals at the indicated dosage.

response curve for sedation to the left along the dose axis in patients was reported by Person et al. (12). However, the authors did not determine the type of interaction. Because the doses of alfentanil they used to supplement midazolam were very high (75 μg/kg bolus + 300 $\mu g \cdot kg^{-1} \cdot h^{-1}$ over 15 min + 65 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for maintenance), simple summation of the sedative effects of alfentanil and midazolam cannot be excluded as a possible outcome of this interaction.

In contrast to the sedative effect, hypnotic benzodiazepine-opioid interaction resulted in a profound synergism. This was found in the present study with the midazolam-morphine interaction and also with the diazepam-morphine interaction determined previously under similar conditions (3). Clinical studies on benzodiazepine-opioid interactions for induction of unconsciousness (hypnotic effect) also demonstrated a highly synergistic interaction (2), which is different from the outcome for sedative effect reported in the above-mentioned study on midazolam-morphine interaction in patients (4). However, the difference between hypnotic versus sedative interaction obtained in these two clinical studies is not definitive enough due to a number of factors that were not identical in the studies: difference in opioids used (alfentanil with hypnosis and morphine with sedation), in patient population (patients from Birmingham, Alabama, with hypnosis and from Safed, Israel, with sedation), and in the investigators. In the present study conditions for comparison of the sedative and hypnotic interactions were very similar (same drugs, subjects, investigators, and time), but the difference between these interactions still was clearly seen. The possibility of producing the above effect in rats gave an advantage as far as the number of subjects is concerned. Assessment of a change in the slope of a dose-response curve requires many more subjects than that for the ED_{50} values; therefore, this analysis is very difficult to perform in patients, but possible to do in rat experiments. Using this advantage, we were able to demonstrate that morphine makes the slope of the midazolam dose-response curve for sedation steeper, indicating a decrease in individual variability to the sedative effect.

Thus, the difference between hypnotic and sedative opioid-benzodiazepine interactions was clearly seen in this study. Analysis of the results obtained by Gamble et al. (1) also indicates that midazolam-opioid interaction for sedation and unconsciousness may be different. They reported that 10 of 20 patients did not open their eyes on command 5 min after midazolam administration (0.3 mg/kg, intravenously); 17 of 20

Table 4. Midazolam-Morphine Hypnotic Interaction

Group	Equieffective doses (ED_{50}) **Fraction** mg/kg Midazolam component	 Morphine component	Sum of fractions	Coefficient of interaction[a]
A. Midazolam	1.00 9.3(4.4,19.4)[b]	0.00	1.00	—
B. Morphine	0.00	1.00 13.0(9.4,18.1)	1.00	—
C. Combination	0.13 1.3(0.7,2.2)	0.14 1.8(1.0,3.1)	0.27	3.70 ($P < 0.0001$)

[a] Measure of interaction representing the ratio of the expected sum of fractions if the drugs are additive (i.e., 1.00) to the obtained sum of fractions. The P-value denotes the significance of the difference from simple summation of the effects.

[b] 95% confidence limits are in parentheses.

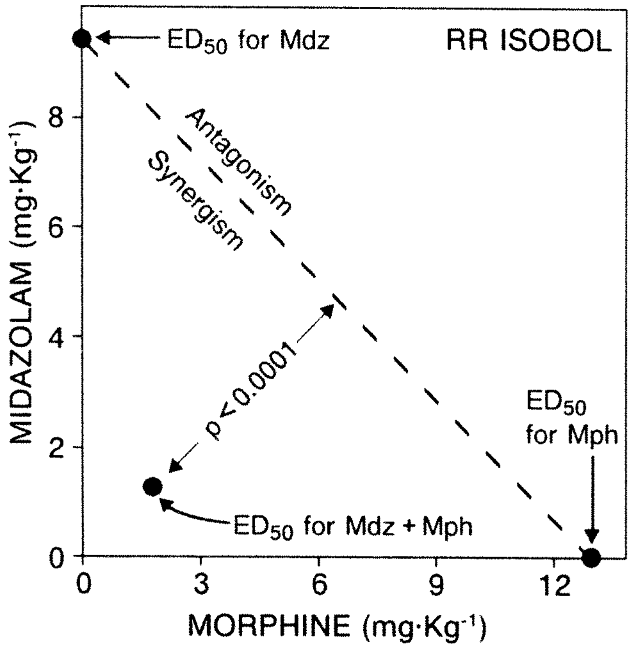

Figure 3. ED_{50} isobologram for the interaction of midazolam (Mdz) and morphine (Mph) as characterized by loss of the righting reflex.

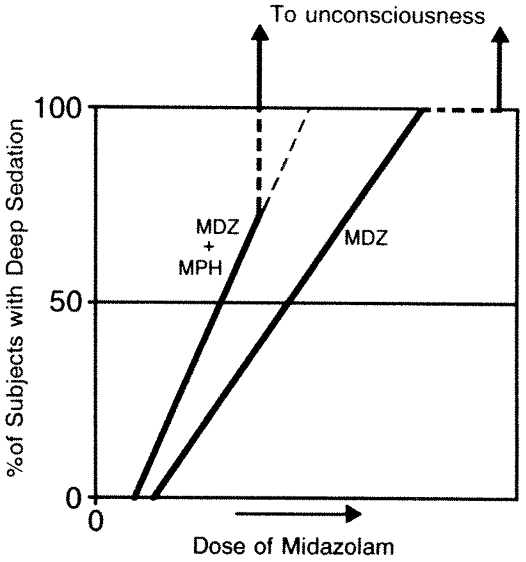

Figure 4. Hypothetical relationship between sedation and unconsciousness with midazolam (MDZ)-morphine (MPH) interaction. See text for explanation.

patients reached the same end point when midazolam (also 0.3 mg/kg) was given with "light opiate" premedication (50–75 mg meperidine per patient, intramuscularly). At the same time, the number of patients who were not at least very drowsy did not significantly change: three of 20 without opioid premedication and two of 20 with it. These results suggest that meperidine does not increase the incidence of transition from light to profound midazolam-induced sedation at least to the same extent as from profound sedation to unconsciousness.

The difference between midazolam-morphine interaction for sedation and unconsciousness may result in a peculiar situation when, in some subjects, unconsciousness will follow moderate sedation as if the process of central nervous system depression on its way to unconsciousness bypasses the stage of deep sedation. Figure 4 illustrates this hypothetical situation when the sedative dose-response curve for midazolam is shifted by the addition of morphine to the left along the dose axis and the curve's upper end cannot be determined because of induction of unconsciousness, representing a different effect also associated with central nervous system depression. Clinical implication of this situation might be that in some patients, despite careful titration of the drug(s), deep conscious sedation is impossible to obtain: unconsciousness will immediately follow the moderate degree of sedation.

The obvious difference in the outcomes of interactions between benzodiazepines and opioids regarding sedative and hypnotic end points observed in animal experiments and in humans cannot be explained by the contribution of ventilatory depression (hypercarbia) in the case of the hypnotic effect (which requires higher doses of interacting agents). With the diazepam-morphine interaction, studied under similar conditions, we obtained the same degree of hypnotic synergism and the Pa_{CO_2} measurements showed the absence of any contributory effect of hypercarbia (3).

Previously reported results with brain-concentration-related analysis of the morphine-diazepam hypnotic interaction demonstrated the same degree of synergism as results with dose-related analysis of the same interaction (3). This outcome decreases the probability that pharmacokinetic factors play a significant role in the morphine-benzodiazepine hypnotic synergism. Differences in the outcomes of the midazolam-morphine interaction regarding sedation and hypnosis suggest that the underlying mechanism for these two effects are different; therefore, they should not be regarded as only increasing depths of the same action.

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1990;71:144–8

Cardiovascular Actions of Common Anesthetic Adjuvants During Desflurane (I-653) and Isoflurane Anesthesia in Swine

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WEISKOPF RB, EGER EI II, HOLMES MA, YASUDA N, JOHNSON BH, TARG AG, RAMPIL IJ. Cardiovascular actions of common anesthetic adjuvants during desflurane (I-653) and isoflurane anesthesia in swine. Anesth Analg 1990;71:144–8.

To determine the cardiovascular actions of drugs commonly combined with inhalation anesthetics, we administered one drug from each of several classes of adjuvants to seven swine already anesthetized with equipotent concentrations (1.2 MAC) of desflurane, formerly I-653, a new inhaled anesthetic, or isoflurane. Succinylcholine (1 and 2 mg/kg), atracurium (0.6 mg/kg), and atropine (5 μg/kg) plus edrophonium (5 mg/kg) had no cardiovascular effects. Fentanyl was given in amounts that decreased MAC for the inhaled anesthetics by 25%–35%. A dose of 50 μg/kg IV had no cardiovascular effects during either anesthetic, whereas 100 μg/kg IV modestly increased systemic vascular resistance without changing other variables. Naloxone (100 μg/kg IV) during infusion of fentanyl decreased systemic vascular resistance and increased cardiac output during both desflurane and isoflurane anesthesia, increased heart rate during only isoflurane anesthesia, and did not affect mean arterial blood pressure during either anesthetic. Thiopental (2.5 and 5.0 mg/kg IV) decreased mean aortic blood pressure, cardiac output, stroke volume, and systemic vascular resistance during both anesthetics without altering heart rate or left- or right-sided cardiac filling pressures. The addition of 60% nitrous oxide caused no cardiovascular changes during desflurane anesthesia, but increased systemic vascular resistance and decreased cardiac output and stroke volume during isoflurane without altering heart rate or cardiac preload. We conclude that the usual clinical doses of adjuvants commonly administered during anesthesia have no untoward cardiovascular actions during 1.2 MAC desflurane or isoflurane anesthesia in swine.

Key Words: ANESTHETICS, VOLATILE—desflurane, isoflurane. ANALGESICS, FENTANYL. NEUROMUSCULAR RELAXANTS, ATRACURIUM, SUCCINYLCHOLINE. ANESTHETICS, GASES—nitrous oxide. ANTAGONISTS, NEUROMUSCULAR—edrophonium. PARASYMPATHETIC NERVOUS SYSTEM, ATROPINE.

Intravenous administration of anesthetic adjuvants is common during inhalation anesthesia. Nitrous oxide (N_2O) and narcotics may be added to decrease the volatile anesthetic requirement or to modify the circulatory response to noxious stimuli; depolarizing and nondepolarizing neuromuscular blocking agents are given to augment relaxation; ultra-short-acting barbiturates are used to induce anesthesia or transiently increase anesthetic depth; anticholinesterases are combined with anticholinergic agents to decrease the intensity of neuromuscular blockade achieved using blockers; and naloxone may be used to antagonize the effects of narcotics. The cardiovascular actions of these drugs alone are known, but their effects during inhalation anesthesia are not, excepting those of N_2O. In this study, we have determined the cardiovascular actions of clinically applied doses of one adjuvant from each of these classes during desflurane and isoflurane anesthesia.

Materials and Methods

With permission from our Committee on Animal Research, we prepared seven female swine (age,

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10–14 wk; weight, 19.4 ± 1.2 kg, mean ± SE) for study by inserting chronically indwelling aortic and 5F thermodilution pulmonary arterial cannulae, as previously described (1). Anesthesia was induced via a mask with desflurane or isoflurane in oxygen and maintained at 1.2 MAC (2). Tracheas were intubated without the aid of neuromuscular blocking agents, and ventilation was controlled at a tidal volume of 20 mL/kg, with frequency adjusted to maintain normocapnia. Core temperature was measured using the pulmonary-artery cannula thermister, and maintained within 0.5 C° of the awake value using circulating hot-water pads, as necessary. All animals were studied once with each anesthetic, randomly ordered. Studies were separated by 5–8 days, and all swine were healthy with normal core temperature for both studies.

End-tidal concentrations of desflurane, isoflurane, and carbon dioxide (CO_2) were measured by infrared analyzers (Puritan-Bennett 222 Anesthetic Agent Monitor and Beckman LB-2, Beckman Instruments) calibrated using secondary (tank) standards (anesthetics) and the method of Scholander (CO_2) (3). End-tidal concentrations, aortic pulmonary arterial, right atrial, and pulmonary capillary wedge pressures obtained from Statham 23 Db transducers, and electrocardiographic data were recorded on a polygraph (Gould Brush model 2800). Inspired oxygen (O_2) concentrations were measured by a polarographic instrument calibrated with room air and 100% O_2. The sum of the inspired concentrations of O_2 and anesthetic concentrations was subtracted from 100% to estimate the concentration of N_2O, when studied.

Cardiac output was determined in duplicate by injection of 3 mL of 0°C, 0.9% NaCl into the right atrium during end-expiration using a thermodilution technique incorporating an analog computer (Edwards model 9200A). A third measurement was obtained if the first two differed by more than 0.2 L/min. We recorded the thermodilution curve to ensure that it was logarithmic. Systemic vascular resistance was estimated as the difference between mean aortic and right atrial blood pressures, divided by cardiac index (cardiac output divided by weight), and pulmonary vascular resistance was estimated as the difference between mean pulmonary arterial and pulmonary capillary wedge pressures, divided by cardiac index.

Cardiovascular variables were first measured after 20 min of stable end-tidal anesthetic concentration, then at the times specified after administration of the following drugs:

1. succinylcholine, 1 mg/kg IV: 20 s, 1, 5, 10 min;
2. succinylcholine, 2 mg/kg IV: 20 s, 1, 5, 10 min;
3. N_2O, 60%: after 30 min of wash-in (following addition of N_2O to 1 MAC desflurane or isoflurane to achieve a total anesthetic potency of 1.2 MAC) (2,4);
4. fentanyl, 50 μg/kg IV + 67 $\mu g \cdot kg^{-1} \cdot h^{-1}$: 5, 10, 15 min ($n = 4$, isoflurane; $n = 3$, desflurane); or
5. fentanyl, 100 μg/kg IV + 134 $\mu g \cdot kg^{-1} \cdot h^{-1}$: 5, 10, 15 min ($n = 3$, isoflurane; $n = 4$, desflurane);
6. naloxone, 100 μg/kg IV: 1, 2, 5, 10, 15 min during the infusion of fentanyl;
7. atracurium, 0.6 mg/kg IV: 1, 5, 15 min;
8. thiopental, 2.5 mg/kg IV: 30 s, 1, 5, 15 min;
9. thiopental, 5 mg/kg IV: 30 s, 1, 5, 15 min;
10. atropine, 5 μg/kg IV plus edrophonium, 0.5 mg/kg IV: 1, 5, 10 min.

Drugs always were given in this order—those with the most evanescent effects were administered first, and the antagonist was given immediately after the agonist in an effort to minimize potential interactions with subsequent drugs. Excepting thiopental, this sequence of drugs represents that typically used in clinical practice (occasionally, thiopental is used toward the end of a procedure to increase anesthetic depth transiently). All cardiovascular variables were allowed to return to the baseline value preceding administration of each drug before administration of the next. Thiopental was not given until a minimum of 1 h had passed since termination of the fentanyl infusion.

Cardiovascular data obtained before (baseline) and after the administration of each dose of each drug were compared using analysis of variance with repeated measures (5). The difference between the values preceding and following adjuvant administration were assessed by paired *t*-tests, with a Bonferroni correction. Statistical significance was accepted at $P < 0.05$.

Results

The cardiovascular actions of desflurane or isoflurane alone (decreased systemic vascular resistance, mean aortic blood pressure, cardiac index, stroke volume index, and increased heart rate) were similar to those reported in other similar swine (1). Succinylcholine (1 and 2 mg/kg IV), atracurium, and atropine plus edrophonium had no significant cardiovascular effects. Fentanyl (100 μg/kg IV) significantly increased systemic vascular resistance during both anesthetics: desflurane from 352 ± 37 to 433 ± 38 mm $Hg \cdot kg \cdot L^{-1} \cdot min^{-1}$; isoflurane, from 388 ± 37 to 478 ± 82 mm $Hg \cdot kg \cdot L^{-1} \cdot min^{-1}$ (although the increase in mean aortic blood

Table 1. Interaction of N_2O With Desflurane and Isoflurane

Variable	Desflurane		Isoflurane	
	Before	During	Before	During
Aortic blood pressure	53 ± 2	53 ± 3	60 ± 3	56 ± 3
Heart rate	109 ± 6	116 ± 6	109 ± 6	108 ± 6
Cardiac output (mL·kg^{-1}·min^{-1})	142 ± 18	139 ± 14	155 ± 16	120 ± 12[a]
Stroke volume (mL/kg)	1.28 ± 0.11	1.19 ± 0.08	1.42 ± 0.12	1.12 ± 0.11[a]
Systemic vascular resistance (mm Hg·kg·L^{-1}·min^{-1})	351 ± 29	353 ± 29	355 ± 21	425 ± 29[a]

[a] Indicates $P < 0.05$ compared to without nitrous oxide.

pressure and the decrease in cardiac index were not statistically significant), but had no cardiovascular effects at the lower dose of 50 μg/kg.

The administration of thiopental and naloxone during both anesthetics, and the addition of N_2O to isoflurane, produced the most wide-ranging significant effects (Table 1). Naloxone (100 μg/kg) decreased systemic vascular resistance and increased cardiac output during both anesthetics; it increased stroke volume during desflurane anesthesia and increased heart rate during isoflurane without changing blood pressure with either anesthetic.

Thiopental (2.5 and 5.0 mg/kg) decreased mean aortic blood pressure, cardiac output, and stroke volume during both anesthetics, without altering heart rate or left- or right-sided cardiac filling pressures (right atrial and pulmonary capillary wedge pressures) (Figure 1).

The addition of 60% N_2O to 1 MAC desflurane (to maintain a total potency of 1.2 MAC) had no cardiovascular effect (Figure 2) but increased systemic vascular resistance and decreased cardiac output and stroke volume during isoflurane anesthesia without changing heart rate, cardiac preload (right atrial and pulmonary capillary wedge pressures), or cardiac afterload (mean aortic and pulmonary arterial blood pressures) (*Figure 2*).

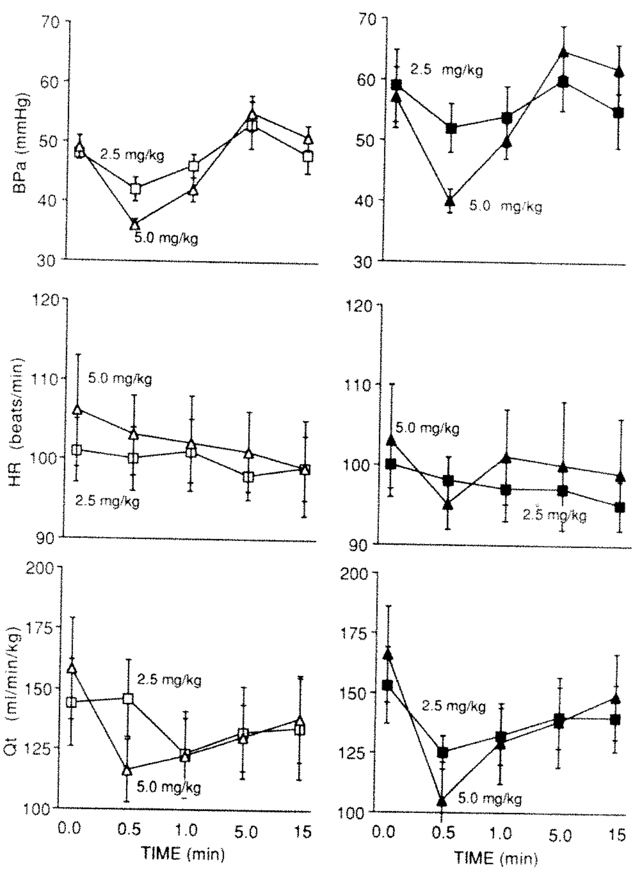

Figure 1. Mean aortic blood pressure (BPa), heart rate (HR), and cardiac output (Qt) during 1.2 MAC desflurane (*open symbols*) and 1.2 MAC isoflurane (*closed symbols*) before (time = 0) and after 2.5 (*squares*) and 5.0 (*triangles*) mg/kg thiopental. Thiopental significantly ($P < 0.05$) decreased BPa and Qt during both desflurane and isoflurane anesthesia, but did not alter HR.

Discussion

Studies of the interactions of anesthetic adjuvant drugs and inhaled anesthetics are uncommon or lacking. We have, therefore, examined the effects of seven commonly used adjuvant drugs during anesthesia with isoflurane, the most popular potent inhalation agent in North America, and desflurane, a new inhalation agent.

Excepting thiopental, we administered adjuvants in the order typically used in clinical practice. By studying sequentially administered drugs, we did not exclude the potential for adjuvant interaction. However, such interactions might be expected in the clinical milieu. To minimize drug interactions we administered those with short half-lives first, and permitted an adequate interval between administrations to dissipate residual effects. We also waited until cardiovascular values returned to those preceding administration of each drug (also, thus, similar to the initial values during anesthesia) before giving the next drug.

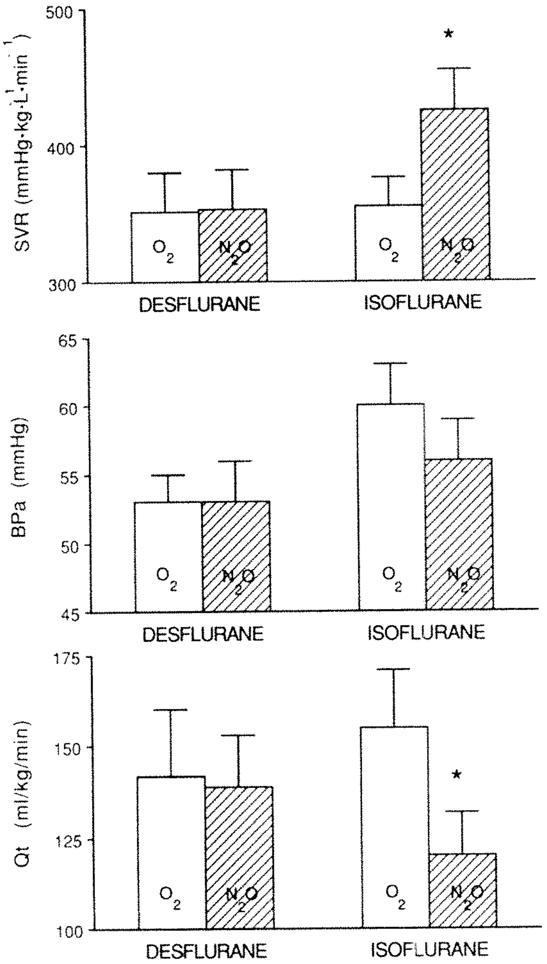

Figure 2. Systemic vascular resistance (SVR), mean aortic blood pressure (BPa), and cardiac output (Qt) during 1.2 MAC desflurane and 1.2 MAC isoflurane anesthesia in O_2 or 60% N_2O. *Indicates values with N_2O differ significantly ($P < 0.05$) from those with O_2.

Our data support the clinical impression that untoward cardiovascular interactions are unlikely to occur with the doses of anesthetic adjuvants commonly used during inhalation anesthesia. Half the drugs tested (succinylcholine, atracurium, atropine plus edrophonium) had no significant effect. The only effect of fentanyl was an increase in systemic vascular resistance during both desflurane and isoflurane anesthesia, which returned resistance to values not different from those in similar conscious swine (450–490 mm Hg·kg·L^{-1}·min^{-1}) (1). Fentanyl increases plasma vasopressin concentration in humans (6), and this action could account for the increase in systemic vascular resistance observed in our swine.

We administered an especially large dose of naloxone to ensure that we antagonized the effects of fentanyl. The resulting cardiovascular changes were consistent with those found in other species given doses of this magnitude (7,8), and were most likely due to increased sympathetic nerve activity, causing release of neural norepinephrine and adrenal epinephrine (7,8). The addition of 60% N_2O to desflurane had no cardiovascular effects, but, when added to isoflurane, it modestly increased (20%) systemic vascular resistance and decreased cardiac output and stroke volume by similar amounts. When added to potent inhaled anesthetics, N_2O increases mean arterial blood pressure, cardiac output, and systemic vascular resistance (except enflurane), both in humans (9–12) and swine (13). However, when added to higher halothane concentrations, which inhibit sympathetic effects, N_2O continues to increase systemic vascular resistance, but causes no change (14) or decreases (9) blood pressure and cardiac output. Our data may indicate that 1.2 MAC desflurane inhibits sympathetic effects better than an equipotent concentration of isoflurane.

Thiopental produced a similar dose-related depression of circulation with both inhalation agents (Figure 1), an effect consistent with its known cardiovascular actions (15,16). However, the interaction of thiopental with inhaled agents may be less innocuous than implied by Figure 1. The initial protocol included administration of a higher dose (10 mg/kg) of thiopental. Administration of this higher dose caused death in one animal given desflurane and profound depression in one given isoflurane. Note that the MAC equivalent for the highest dose of thiopental represented in Figure 1 (5 mg/kg = 0.45 MAC; the MAC equivalent for thiopental in swine is 11 mg/kg) (17) exceeds the fraction of MAC represented by 60% N_2O in the animals (0.21 MAC; the MAC of N_2O in swine is 280%) (4).

Extrapolating our findings to humans requires caution. Thiopental and N_2O have less anesthetic effect (are less potent) in swine than in humans. Fentanyl (50 μg/kg) decreases MAC for desflurane and isoflurane in swine by only 25%–35% (Weiskopf RB, Eger EI II, Holmes MA, et al.: unpublished data), but has greater effect in humans. Thus, the adjuvant doses we have tested in swine may have a greater cardiovascular effect in humans. Similarly, where we saw no effect, some may occur in humans. Previous reports suggest that some effect might have been expected where we saw none. For example, repetitive administration of succinylcholine can produce bradycardia, and atracurium can cause hypotension (18), probably by causing histamine release.

Another limitation of our study is that we examined adjuvant interactions with only one dose of inhaled anesthetic. Although we would expect qualitatively similar results at different anesthetic potencies, quantitative effects would be likely to differ. That is, we would anticipate a far more profound effect of thiopental during 2 MAC of either isoflurane and desflurane, but we did not test this possibility.

We conclude that the usual clinical doses of commonly used anesthetic adjuvant drugs do not have untoward cardiovascular effects during 1.2 MAC desflurane and isoflurane anesthesia.

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Mechanism of Action of Local Anesthetics on Synaptic Transmission in the Rat

Mahmood Tabatabai, MD, PhD, and August M. Booth, PhD

TABATABAI M, BOOTH AM. Mechanism of action of local anesthetics on synaptic transmission in the rat. Anesth Analg 1990;71:149–57.

The mechanism of action of local anesthetics on synaptic transmission and their effects on synaptic components and on electrophysiologic properties of the nerve cell body are not clear. Therefore, the effects of lidocaine and bupivacaine on pre- and postsynaptic mechanisms underlying synaptic transmission in sympathetic ganglia were studied utilizing the techniques of intracellular recording and stimulation on isolated superfused superior cervical ganglia of rats. Lidocaine and bupivacaine either depressed or completely blocked synaptic transmission in sympathetic ganglia in a dose-dependent manner. Blockade of axonal conduction in presynaptic fibers was preceded by increased latency (the latency increased from 11.2 ± 0.9 to 16.5 ± 1.4 ms, mean ± SEM, $P < 0.01$) when the drugs were applied to the presynaptic nerves. Application of the drugs directly to the ganglion produced alterations in postsynaptic membrane properties consisting of decreased membrane resistance (from 40 ± 3 to 32 ± 3 MΩ, $P < 0.01$), increased firing threshold (from 14 ± 0.5 to 18 ± 0.5 mV, $P < 0.01$), and decreased action potential amplitude ($P < 0.01$) and/or blockade of action potential generation. Resting postsynaptic membrane potential did not change significantly. These changes were reversible. However, even after the excitatory postsynaptic potential resulting from presynaptic nerve stimulation had fully recovered during washout of the local anesthetic, the threshold for evoking the spike potential (firing level) still remained elevated for both presynaptic and intracellular stimulation of the ganglion cell, suggesting prolonged cell depression. The decreased membrane resistance and prolonged depression of the ganglion cell outlasted the effects of the drugs on the preganglionic components by more than a factor of 2. The postganglionic compound action potential was depressed or abolished according to the anesthetic dose used. High frequency stimulation (5–15 Hz) of the preganglionic fibers caused significant reduction ($P < 0.05$) of the postganglionic compound action potential amplitude in the presence of the local anesthetics, suggesting possible depression of the synaptic processes such as transmitter release.

The results show that lidocaine and bupivacaine can produce reversible dose-dependent depression and/or blockade of synaptic transmission in the sympathetic ganglia of the rat by (a) blockade of axonal conduction in the presynaptic fibers; (b) depression of the postsynaptic cells; and (c) depression of the transmitter release. The prolonged action of the anesthetics on the postsynaptic cells suggests that sympathetic function may remain compromised well beyond the time necessary for the return of the axonal conduction. Lidocaine and bupivacaine produced similar effects even though in equimolar quantities the duration of action of bupivacaine was 2–3 times longer than that of lidocaine.

Key Words: ANESTHETICS, LOCAL—lidocaine, bupivacaine. SYMPATHETIC NERVOUS SYSTEM, SYNAPTIC TRANSMISSION—local anesthetic effects.

The mechanism of action of local anesthetics on synaptic transmission and their effects on synaptic components have not been adequately studied. Likewise, the effects of local anesthetics on electrophysiologic properties of the nerve cell soma have not been investigated in detail. Curtis and Phillis studied the effects of iontophoretic application of procaine on the spinal motoneurons in cats lightly anesthetized with sodium pentobarbital (1). They found that procaine suppressed the spike potential of the neurons elicited by orthodromic stimulation without altering the excitatory postsynaptic potentials (EPSPs) and the membrane resistance. Aceves and Machne, using isolated dorsal root ganglia of the spinal cord of frogs, confirmed the depressant action of procaine on spike potential generation evoked by direct stimulation of the ganglion cells (2).

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In the present study, the effects of the local anesthetics lidocaine and bupivacaine on pre- and postsynaptic components underlying synaptic transmission in sympathetic ganglia were studied using techniques for intracellular recording and stimulation. The effects of these local anesthetics on electrophysiologic properties of the nerve cell soma were verified. Our results indicate that lidocaine and bupivacaine block synaptic transmission in sympathetic ganglia of the rat, and that the postsynaptic cells are the last to recover from the depressant actions of these agents. Local anesthetics abolish both the postsynaptic spike potential and, in larger doses, the EPSPs, while the membrane resistance is concurrently reduced. Evidence is presented that suggests a depressant action of these anesthetics on synaptic processes such as transmitter release. This study also allows comparison of the effects of lidocaine and bupivacaine on synaptic transmission and on electrophysiologic properties of the nerve cells in the sympathetic ganglia.

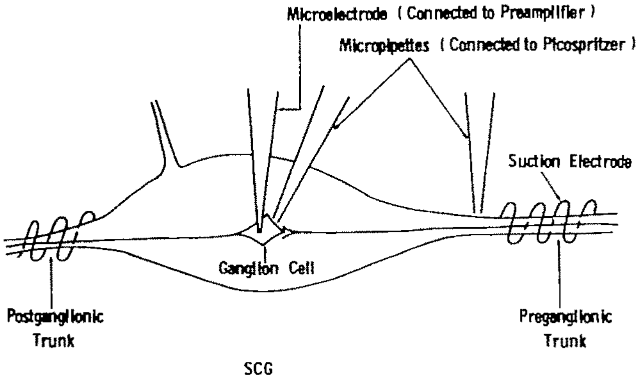
Microelectrode (Connected to Preamplifier)
Micropipettes (Connected to Picospritzer)
Suction Electrode
Ganglion Cell
Postganglionic Trunk
Preganglionic Trunk
SCG

Figure 1. Schematic diagram of the experimental method using the superior cervical ganglion (SCG) with the pre- and postganglionic trunks. A microelectrode is shown impaling a cell. It can record from and stimulate the cell. The pre- and postganglionic trunks have been drawn into suction electrodes. The one around the preganglionic trunk is used for orthodromic stimulation of the ganglion cells. The one around the postganglionic trunk is used to record the postganglionic nerve trunk CAP. Micropipettes are used for pressure ejection of lidocaine and bupivacaine onto selective areas of the preparation within the tissue bath.

Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee. Rats of either sex, weighing 200–500 g, were anesthetized with Dial urethane intraperitoneally (each milliliter Dial urethane contains 100 mg diallylbarbituric acid, 400 mg urethane, 400 mg monoethyl urea). Using a dissecting microscope, the superior cervical ganglia of 10 rats, along with the pre- and postganglionic trunks, were removed and mounted in a tissue bath (Figure 1), superfused continuously at a rate of 3 mL/min with Krebs–Ringer solution, and bubbled with a mixture of 95% oxygen and 5% carbon dioxide at a pH of 7.2. The tissue bath had a volume of 10 mL. The superior cervical ganglion is a sympathetic ganglion. The composition of Krebs–Ringer solution, in mmol/L, was as follows: NaCl, 117.80; KCl, 4.78; KH_2PO_4, 1.16; $MgSO_4$ 7 H_2O, 1.16; dextrose, 11.00; $NaHCO_3$, 24.64; $CaCl_2$ 2 H_2O, 2.53. The bath temperature was maintained between 35.5° and 37°C. The pre- and postganglionic trunks were drawn into suction electrodes. A glass micropipette (microelectrode) with a resistance of 20–40 MΩ was inserted into the ganglion with the aid of a micromanipulator until it impaled a cell, as indicated by the appearance of a resting membrane potential of 40 mV or more on an oscilloscope. The output from the microelectrode was amplified, displayed on the oscilloscope, and stored on magnetic tape. The microelectrode served to record from and/or to stimulate the cell directly. The stimulus source for direct cell stimulation was a pulse generator that could deliver depolarizing and hyperpolarizing pulses to the cell in nanoamperes (nA) at a frequency of 5 Hz. The duration of each pulse was 20–40 ms. (For further details, see Reference 3.)

The preganglionic (presynaptic) fibers were stimulated electrically with square wave pulses through the suction electrode, while recording from the cell via the microelectrode, and from the postganglionic (postsynaptic) fibers via the other suction electrode (Figure 1).

The characteristics of the stimulus applied to the preganglionic fibers were as follows: stimulus strength, 3–15 V; pulse duration, 0.2–0.5 ms; frequency, 1 Hz. For high frequency stimulation of the preganglionic fibers, the frequencies applied were 5, 10, and 15 Hz. For recording compound action potential (CAP) from the postganglionic fibers, the output from the postganglionic suction electrode was amplified and displayed on the oscilloscope. Thus, the following responses were monitored and recorded simultaneously:

(a) postganglionic CAP elicited by electrical stimulation of the preganglionic nerve fibers;
(b) synaptic responses, i.e., EPSPs and action potential (AP) of single ganglion cells evoked by stimulation of preganglionic fiber(s); and
(c) the direct response of the cell to intracellular current injection.

From these recordings, the following electrophysiologic variables were measured for the postsynaptic

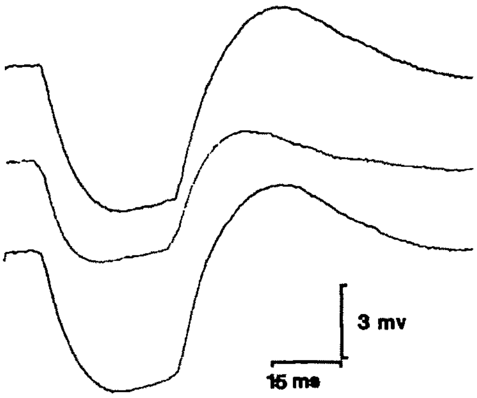

Figure 2. Measurement of membrane resistance (R) by intracellular hyperpolarizing current injection. Each trace shows the membrane potential change of the same ganglion cell and represents the averaged response to 20 hyperpolarizing pulses of 30 ms and 0.1 nA, delivered at a frequency of 5 Hz. In each trace, the initial left horizontal line depicts resting membrane potential. When the hyperpolarizing pulse is applied, the downward deflection results indicating membrane hyperpolarization. Upon termination of the 30-ms hyperpolarizing pulse, an upward deflection results. By measuring the maximal membrane potential change (ΔV) resulting from 0.1 nA current (I), R is calculated from Ohm's law, where $R = \Delta V/I$. The *top trace* was obtained before drug application. The calculated R was 60 MΩ. The *middle trace* was obtained 40 s after focal application of 400 nmol of lidocaine to the ganglion by pressure ejection, and shows R to be 44 MΩ. The *bottom trace* was obtained following 15 min of washout after lidocaine application, where R is 57 MΩ.

cell: resting membrane potential (RMP), action potential amplitude, duration of AP at 50% of maximal amplitude (APD_{50}), latency of EPSPs, firing threshold (the depolarization in millivolts necessary to evoke an AP) for both presynaptic and intracellular stimulation, and membrane resistance. The amplitude of the pre- and postganglionic CAP was also measured. Membrane resistance was determined by applying an hyperpolarizing current (0.1 nA for 20–40 ms) to the cell and observing the RMP change (ΔV). According to Ohm's law, $\Delta V = R \times I$, where R represents resistance and I current. Knowing ΔV and I, the resistance was calculated (Figure 2).

To show the effects of the local anesthetics on the preganglionic nerve fibers, the preganglionic nerve trunk was dissected out and drawn into suction electrodes inside the tissue bath. In this case, one suction electrode stimulated one end while another suction electrode recorded CAP from the other end of the nerve trunk.

Preservative-free lidocaine hydrochloride and bupivacaine hydrochloride were dissolved in Krebs–Ringer solution and delivered to the tissue bath by pressure ejection technique using micropipettes and a Picospritzer (Figure 1), by superfusion, or through a polyethylene tube (PE-20). When pressure ejection was employed, microliter quantities of a 10 or 30 mM (millimolar) solution (0.28% and 0.84%, respectively) of the anesthetics could be delivered. Each microliter of the 10 and 30 mM solutions had 10 and 30 nmol of the anesthetics, respectively. When superfusion was employed, 100 mL of 100 μM solution of lidocaine (1 mL of this solution = 100 nmol lidocaine), or 100 mL of 50 μM solution of bupivacaine (1 mL of this solution = 50 nmol bupivacaine) was used and found effective in blocking the cell response to presynaptic stimulation. When a polyethylene tube was used to deliver the anesthetics to the tissue bath, 0.1–0.2 mL of various millimolar concentrations, containing different nanomole quantities of the local anesthetics, was delivered. Initially, we administered the local anesthetics to the tissue bath via a polyethylene tube to arrive at an effective dose, i.e., one that would suppress or block synaptic transmission. Then we employed superfusion to provide a uniform concentration of the drugs throughout the tissue bath. Finally, pressure ejection was used to deliver the local anesthetics selectively at specific sites of the preparation. The data presented in Results are based on the use of pressure ejection. However, the dose-response relationship for the effects of the local anesthetics on the postganglionic compound action potential is based on the delivery of the anesthetics to the tissue bath at the junction of the preganglionic fibers and the ganglion via a polyethylene tube.

Application of the drugs to the preparation was randomized with respect to the drug type and concentration, interspersed with application of the control solution (Krebs–Ringer solution). When the electrophysiologic properties of the ganglion and cell returned to the predrug (control) values, another drug trial was made. Once drug trials were completed on a cell, or in the event the cell was lost, a new cell was impaled and the above steps were repeated. The ganglia remained in stable physiologic condition for at least 24 h. The criterion for the stable physiologic condition was the presence of cells with RMP of 40 mV or greater that could be fired with an intracellular current of less than 0.5 nA.

Results are expressed as mean ± SEM. Student's paired t-test was used to analyze the data. For comparison of the percent depression of the postganglionic CAP amplitude in response to various doses of lidocaine and bupivacaine, the nonparametric Mann–Whitney test was employed, and for comparison of the percent depression of postganglionic CAP in response to high frequency stimulation before and after treatment with bupivacaine, the nonparametric Walsh test was used. P values of less

Table 1. Effects of Lidocaine (400 nmol) on Electrophysiologic Properties of the Nerve Cell Soma in the Superior Cervical Ganglion of the Rat

	Before	After	*P*
RMP (mV)	51.0 ± 2.4	51.8 ± 3.6	>0.05
APA (mV)	75.0 ± 3.0	17.0 ± 2.0	<0.01
APD_{50} (ms)	1.3 ± 0.05	2.2 ± 0.05	<0.01
Firing threshold (mV)			
Direct stimulation	13.5 ± 0.5	17.5 ± 0.5	<0.01
Presynaptic stimulation	14.0 ± 0.5	18.0 ± 0.5	<0.01
Membrane resistance (MΩ)	40.0 ± 3.0	32.0 ± 3.0	<0.01
Membrane conductance (mmho)	$1/(40 \times 10^3)$	$1/(32 \times 10^3)$	<0.01
Intracellular current threshold to fire the cell (nA)	0.3 ± 0.05	0.78 ± 0.2	<0.01

APD_{50}, action potential duration at 50% of maximal amplitude; APA, action potential amplitude; RMP, resting membrane potential.

Values are mean ± SEM. Number of cells studied for each parameter varied from 15 to 22. (Two hundred nanomoles of bupivacaine produced almost similar effects and achieved the same level of statistical significance.)

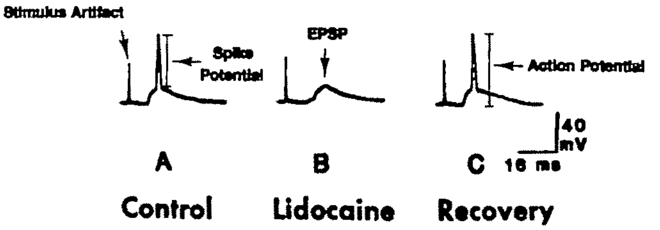

Figure 3. Effects of lidocaine on cell response to presynaptic nerve stimulation. *Panel A* is before application of lidocaine. *Panel B* is 30 s after application of 200 nmol of lidocaine by the Picospritzer through a micropipette near the ganglion. The spike potential was blocked, but the EPSP was spared and never disappeared. *Panel C* shows recovery of the spike potential as a result of the washout of lidocaine via the circulating perfusate. Each AP is preceded by a stimulus artifact that is unaffected by the local anesthetic.

than 0.05 ($P < 0.05$) were considered statistically significant.

Results

Application of lidocaine and bupivacaine to the preparation by any of the techniques described above produced gradual and reversible depression of axonal conduction, synaptic transmission, and postsynaptic (ganglion) cell membrane excitability. The effects on each component will be presented separately in the following sections. A total of 22 cells were studied.

Effects of Anesthetics on Cell Response to Stimulation of the Preganglionic Fibers

The postsynaptic (ganglion) cell responses to electrical stimulation of the preganglionic nerve fibers recorded via the intracellular microelectrode were EPSPs and an AP, and were depressed or blocked by the local anesthetics. The firing threshold for the cells was 14 ± 0.5 mV. Lidocaine (400 nmol) and bupivacaine (200 nmol) increased the firing threshold to 18 ± 0.5 mV ($P < 0.01$) (Table 1) and diminished the rate of rise of AP (as reflected by an increase in the APD_{50} from 1.3 to 2.2 ms) before the AP generation was completely blocked.

Figure 3 shows the effects of lidocaine (200 nmol) on postsynaptic cell response to stimulation of the preganglionic nerve fibers. The spike potential was blocked while the EPSP was spared. When the amount of lidocaine was increased to 400 nmol, the EPSP disappeared too. These changes were reversible, but recovery of spike potential lagged behind that of EPSP in time by at least a factor of 2, suggesting a return of axonal conduction while the cell was still depressed.

Effects of Anesthetics on Ganglion Cell Response to Intracellular Current Injection

Depolarization of the postsynaptic cell membrane by intracellular current injection induced an AP (Figure 4). The firing threshold was 13.5 ± 0.5 mV (Table 1), which was statistically indistinguishable from the firing threshold determined on stimulation of the preganglionic nerve fibers (14 ± 0.5 mV). The current threshold required to depolarize the cells to their firing threshold was 0.3 ± 0.05 nA. Application of the anesthetics abolished the cell response (i.e., AP) to intracellular current injection (Figure 4), and/or raised the current threshold. Figure 5 exemplifies the effect of the anesthetics on the current threshold required to fire a cell. Before application of bupivacaine, the cell could be stimulated with 0.42 nA current. After exposure to bupivacaine (200 nmol) the cell response to current injection was abolished; increasing the current to 1.5 nA failed to elicit any response 2 min after bupivacaine administration. At 7 min, 0.6 nA generated an AP, and, at 12 min, 0.5 nA was required to fire the cell. After 20 min of washout, the cell recovered from the effect of the anesthetic, and 0.42 nA was sufficient to fire the cell. Lidocaine also increased the threshold for stimulation of the cell by intracellular current injection. The intracellular current threshold of 0.3 ± 0.05 nA increased to 0.78 ± 0.2 nA after application of 400 nmol lidocaine or 200 nmol bupivacaine ($P < 0.01$). Therefore, it may be

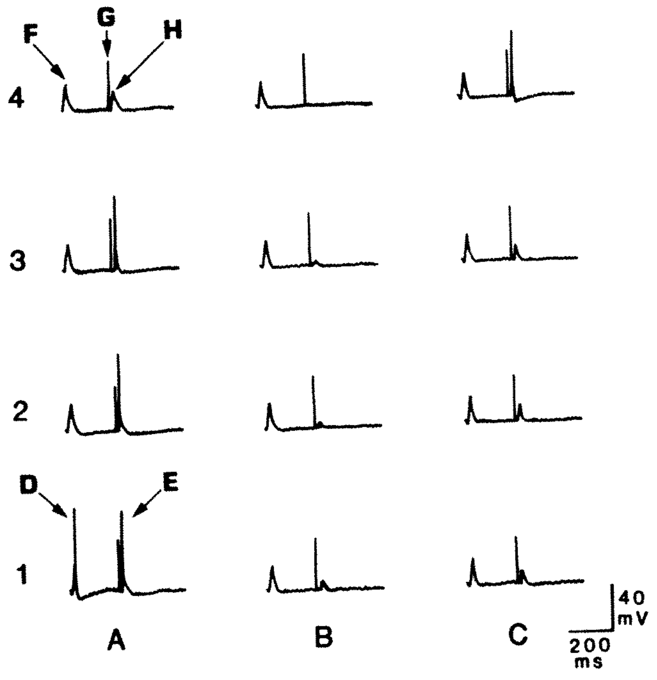

Figure 4. Sequential oscilloscope tracings of the effects of bupivacaine (200 nmol) on a cell's response to presynaptic and intracellular stimulation. Panel A1 is the control and shows the cell response to intracellular current injection on the left (*D*), and to presynaptic stimulation on the right (*E*). The latter is preceded by the stimulus artifact (*G* in panel A4). In panels A2 and A3, the action potential elicited by intracellular stimulation has disappeared, while the response to presynaptic stimulation remains. In panel A4, the presynaptically evoked spike potential disappears, while the EPSP (H) is spared. The EPSP is diminished in panels B1–3 and disappears in panel B4. Recovery of the EPSP occurs in panel C1, and of the action potential in C4. The response to intracellular stimulation has not yet recovered. *D*, action potential due to intracellular depolarizing current injection; *E*, action potential due to presynaptic stimulation; *F*, potential change due to intracellular depolarizing current injection; *G*, stimulus artifact; and *H*, EPSP due to presynaptic stimulation.

concluded that both of the anesthetics decrease the postsynaptic cell excitability.

The decreased excitability of the cell, evidenced by failure of spike potential generation upon intracellular current injection, or presynaptic nerve stimulation in the presence of fully recovered EPSP, lasted at least twice as long as the presynaptic effects of the anesthetics.

Similar results were observed when the preparation was superfused with lidocaine (100 μM solution) or bupivacaine (50 μM solution) at 3 mL/min. The spike potential in response to presynaptic or intracellular stimulation disappeared first; the EPSP disappeared last. When superfusion with lidocaine or bupivacaine was discontinued, EPSP was the first to reappear, followed by spike potential evoked by EPSP or intracellular stimulation. Here, too, it took more than twice as long for the spike potential to recover compared with EPSP recovery.

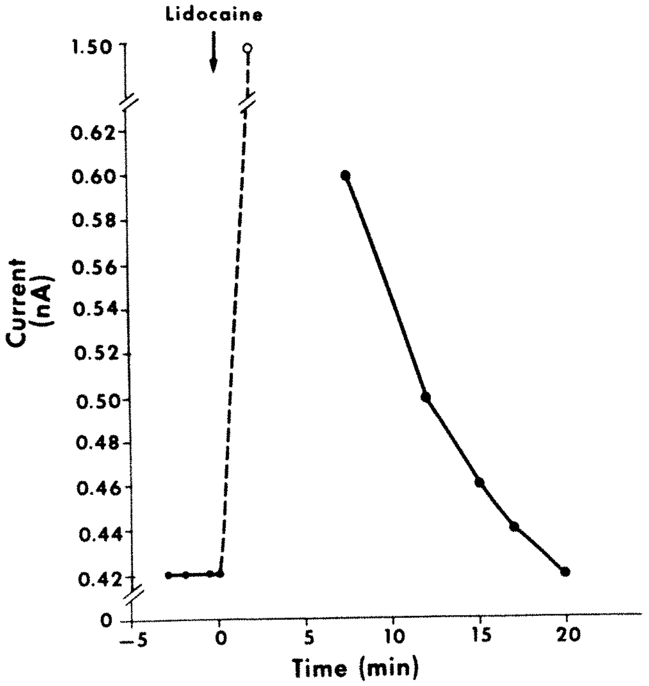

Figure 5. Effects of bupivacaine (200 nmol) on intracellular current threshold (*ordinate*) for postsynaptic cell stimulation. Before bupivacaine, the cell could be fired with 0.42 nA. Two minutes after bupivacaine, even 1.5 nA failed to fire the cell (*dashed line*). At 7 min, 0.6 nA fired the cell. By 20 min, the required current to generate an AP was back to 0.42 nA, indicating cell recovery from the depressant effects of bupivacaine.

Effects of Anesthesia on Resting Membrane Potential, Action Potential Amplitude and Duration, and Membrane Resistance

The RMP of the superior cervical ganglion cells, 51 ± 2.4 mV, was unaffected by lidocaine and bupivacaine (Table 1). The AP amplitude was 75 ± 3 mV. Threshold doses of lidocaine and bupivacaine (nanomole quantities sufficient to increase the firing threshold of the cell, 100 and 50 nmol, respectively), delivered by pressure ejection technique, had minimal effect on the AP amplitude. However, when larger doses (4–6 times the threshold) were used, the AP amplitude decreased, followed by failure of spike generation. The predrug APD_{50} was 1.3 ± 0.05 ms. After drug administration, it increased to 2.2 ± 0.05 ($P < 0.01$) (Table 1).

The membrane resistance of the cells was 40 ± 3 MΩ. Lidocaine (400 nmol) and bupivacaine (200 nmol) reduced the membrane resistance by 20% (32 ± 3 MΩ, $P < 0.01$), thus increasing the membrane conductance by 20% at the time of maximal cell depression. Like the decrease in excitability of the cell with intracellular current injection and presynaptic stimulation, the change in membrane conductance outlasted by more than a factor of 2 other effects of

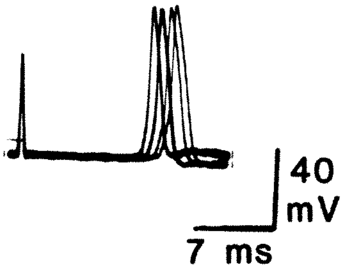

Figure 6. Lidocaine (150 nmol), when selectively applied to the presynaptic fiber, increased the latency of the postsynaptic cell response to presynaptic nerve stimulation, indicating slowing of the axonal conduction in the presynaptic fiber. Of the four APs displayed, each successive one appears later than the preceding one, such that the last AP appears 3 ms after the first one. Note that the stimulus artifacts are all superimposed on each other (left-hand side of the tracing).

the anesthetics on the preparation such as those on axonal conduction and EPSP generation.

Effects of the Anesthetics on Preganglionic Nerve Fibers

As stated earlier, stimulation of the preganglionic fibers evoked EPSPs and an AP in the postsynaptic cell and generated a CAP in the preganglionic fibers. Application of the anesthetics to the preganglionic nerve trunk by pressure ejection resulted in increased latency (from 11.2 ± 0.9 to 16.5 ± 1.4 ms, $P < 0.01$) (Figure 6), indicating slowing of axonal conduction in the preganglionic fibers.

Effects of Anesthetics on Postganglionic Compound Action Potential

Electrical stimulation of the preganglionic fibers resulted in development of CAP in the postganglionic fibers (Figure 7). Depending on the amount of anesthetic used, the CAP either diminished in amplitude or disappeared (Table 2). After a period of blockade, varying from seconds to more than 30 min (the former when nanomoles of anesthetics were applied by pressure ejection, the latter when 0.1–0.2 mL of 10 mM anesthetic solution was applied via the polyethylene tube into the tissue bath), the CAP returned and gradually increased in amplitude until it reached the control value achieved before the anesthetic application.

High frequency stimulation (5, 10, and 15 Hz) of the preganglionic fibers produced depression of the postganglionic action potential, but the degree of depression was greater (by a factor of 2) in the presence of the anesthetics (Figure 7 and Table 3).

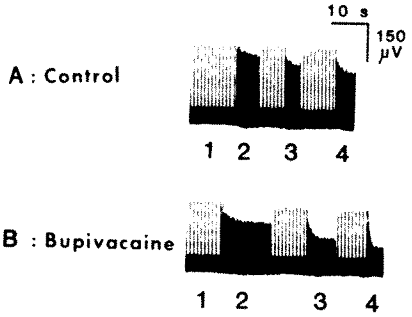

Figure 7. Effect of stimulus frequency applied to preganglionic nerves on postganglionic CAP in control (*panel A*) and bupivacaine-treated preparation (*panel B*). Stimulus frequency at 1 is 1 Hz, at 2 is 5 Hz, at 3 is 10 Hz, and at 4 is 15 Hz. With the frequency of 1 Hz, each AP achieves the same amplitude both in control and bupivacaine-treated preparation. With other frequencies, there is a gradual depression of the AP amplitude such that with the frequency of 15 Hz, the AP amplitude is reduced by 30% before bupivacaine (control) and by 60% after bupivacaine. The difference might be due to a decrease in the transmitter release in the bupivacaine-treated preparation.

Table 2. Percent Depression of the Compound Action Potential Amplitude of the Postganglionic Fibers Resulting From Various Doses of Lidocaine (A) and Bupivacaine (B), Delivered to the Tissue Bath via Polyethylene Tube

	50 nmol	150 nmol	450 nmol
A	0.0 ± 0.0	21.7 ± 1.7	55.8 ± 2.7
B	5.5 ± 1.9	45.5 ± 4.1	97.2 ± 1.4

Numbers are mean ± SEM, $n = 6$. Using the nonparametric Mann–Whitney test, the values are significantly different from each other within each group (i.e., lidocaine-treated group, A; or bupivacaine-treated group, B) ($P < 0.005$) and between the two groups ($P < 0.005$). Comparison of the mean values under the 50-nmol column showed significance at $P < 0.03$.

Table 3. Effect of High Frequency Stimulation of Preganglionic Fibers on Postganglionic Compound Action Potential Amplitude Before and After Treatment With Bupivacaine

	1 Hz	5 Hz	10 Hz	15 Hz
Before bupivacaine	100 ± 0.0	88 ± 1.0	78 ± 0.9	69 ± 1.8
After bupivacaine	100 ± 0.0	72 ± 2.2	44 ± 1.7	29 ± 1.4
P		<0.05	<0.05	<0.05

The numbers are mean ± SEM of five experiments ($n = 5$), and show amplitude as percent of control at 1 Hz. The nonparametric Walsh test shows that at any high frequency, the amplitude is significantly less after bupivacaine than before bupivacaine ($P < 0.05$).

Differences Between the Effects of Lidocaine and Bupivacaine

Qualitatively, lidocaine and bupivacaine had similar effects on the pre- and postsynaptic mechanisms; both depressed or blocked axonal conduction, increased latency for EPSP appearance, raised the firing threshold of the ganglion cell, depressed or abolished ganglion cell response to preganglionic nerve stimulation and intracellular current injection, elevated intracellular current threshold for ganglion cell stimulation, had no effect on RMP, increased cell membrane conductance, and diminished or abolished CAP in the pre- and postganglionic trunks. Quantitatively, bupivacaine was 2–3 times more potent than lidocaine and had a duration of action 2–3 times longer than that of lidocaine.

Discussion

The effects of local anesthetics on axonal conduction (4–8) and neuromuscular transmission (9–11) have been reported. There are also several studies on the effects of these agents on spontaneous and evoked activity of the cortical and subcortical neurons and inhibitory and excitatory pathways within the brain and spinal cord (12–16). The present investigation deals with the mechanism of action of lidocaine and bupivacaine on synaptic transmission in sympathetic ganglia and their effects on electrophysiologic properties of the nerve cell soma itself. The results show that lidocaine and bupivacaine can produce gradual, reversible, and dose-dependent depression and/or blockade of the synaptic transmission in the sympathetic ganglia of the rat, and that the nerve cell soma is a major site of the depressant action of these agents.

In our preparation, recovery of the axonal conduction and synaptic transmission is primarily due to the washout of the local anesthetics from the tissue bath via the anesthetic-free circulating perfusate. Once concentration of the local anesthetics in the tissue bath becomes less than that in the preparation, i.e., the ganglion and its pre- and postganglionic trunks, the local anesthetics will diffuse out of the preparation into the bath and wash out.

Synaptic transmission can be affected by blockade of axonal conduction in the preganglionic fibers, by depression of the transmitter release or receptor sensitivity at the synapse, and, finally, by depressed excitability of the postsynaptic (ganglion) cell. Although these effects can occur together when the tissue is bathed in a solution containing a uniform concentration of local anesthetic, it was possible to evoke selectively drug responses in different regions within the ganglia by focal application of the local anesthetics to the tissue.

The increase in latency observed upon application of local anesthetics to the preganglionic nerves reflects a slowing of the axonal conduction in the preganglionic nerves. The drug effect on the preganglionic nerves was further confirmed by decreased amplitude or abolition of the CAP of the preganglionic nerves in the presence of the anesthetics.

The anesthetic-induced increases in the firing threshold and in the amount of the intracellular current required to generate an AP indicate the direct depressant effects of the drugs on the excitability of the ganglion cells (postsynaptic cells). Failure of spike potential generation upon intracellular current injection or presynaptic nerve stimulation in the presence of fully recovered EPSP indicates increased sensitivity of the postsynaptic cells to the local anesthetics used compared with the presynaptic nerve fibers. Similar results have been reported for somatic afferent neurons by Frumin et al. (17), who showed that the dorsal root ganglia could be blocked by spinal fluid concentrations of procaine that had little or no effect on impulse conduction in the dorsal nerve roots, indicating that the dorsal root ganglia cells were the sensory intrathecal elements most sensitive to the action of procaine (17). Another indication of the direct action of the anesthetics on the cells is the decrease (20%) in cell membrane resistance (or increase in the cell membrane conductance). The effects on the postsynaptic cells, especially the increase in membrane conductance and the decrease in excitability in response to intracellular current injection and presynaptic stimulation, lasted more than twice as long as other effects of the drugs. The prolonged postsynaptic cell depression suggests that sympathetic function may remain compromised well beyond the time necessary for the return of the axonal conduction. The decreased membrane resistance is in contrast to the conclusion reached by Curtis and Phillis in their studies of the effects of procaine on spinal motoneurons (1). Although they did not measure the cell membrane resistance directly, based on the observation that the postsynaptic potentials, i.e., EPSP and inhibitory postsynaptic potential, were unchanged, they concluded that the resistance was altered but little by procaine (1). In a recent publication, Puil and Gimbarzevski report the effects of some inhalation anesthetics on membrane properties of trigeminal sensory neurons in decerebrate guinea pigs (18). They found that endotracheal administration of isoflurane (3%–4%) increased the membrane conductance by 20%. Halothane (2%) produced similar changes but to a lesser extent. The similarity between the effects of the local anesthetics lidocaine and bupivacaine and those of the general anesthetics isoflurane and halothane on the membrane conductance is striking, although their mechanism of action may be different.

Local anesthetics are known to block Na^+ channels (6–8). The decrease in the membrane resistance on the other hand indicates that some membrane channels, perhaps calcium channels, potassium channels, or chloride channels, are opened by the local anesthetics. Our experiments did not investigate the mechanism(s) for the decrease in the membrane resistance.

The postsynaptic cell spike potentials and, in larger doses, the EPSPs, were abolished by lidocaine and bupivacaine. This finding is at variance with the findings of Curtis and Phillis (1), who did not find changes in EPSPs produced by procaine but did observe blockade of the spike potentials. The discrepancy between their findings and ours may be due to the amount of local anesthetic used. Had they applied larger doses, the EPSPs might have been abolished.

The gradual decrease in the size of the EPSP and its final abolition by lidocaine and bupivacaine may have several underlying mechanisms. The ionic basis for an EPSP is that the excitatory transmitter, i.e., acetylcholine, released by the presynaptic nerve fibers, binds to its receptors at the postsynaptic cell membrane to trigger opening of Na^+ channels (19). This is followed by movement of Na^+ along its electrochemical gradient into the cell, causing an EPSP whose amplitude depends on the amount of Na^+ moving into the cell. If Na^+ influx is great enough, the firing threshold is reached and an action potential results (19). Lidocaine and bupivacaine block conduction in the preganglionic fibers, decrease the neurotransmitter release at the synapse, and may decrease the sensitivity of the postsynaptic cell receptors to the neurotransmitter while blocking the Na^+ channels in the postsynaptic cell. All these mechanisms will lead to decreased Na^+ influx into the postsynaptic cell during presynaptic nerve stimulation, thus *reducing* the EPSP amplitude or abolishing it.

The RMP of the postsynaptic cells was not affected by the anesthetics. This finding is consistent with the findings of other investigators on the effects of local anesthetics on isolated nerves (4,5) and spinal cord motoneurons (2).

The dose-related drug enhancement of frequency-dependent ganglionic blockade might suggest that local anesthetics decrease transmitter release at the synapse. This view is supported by a study of the effects of procaine on neuromuscular transmission in the rat phrenic nerve-diaphragm preparation. During high frequency stimulation of the phrenic nerve, reduction of the end-plate potential and failure of transmission occurred (10). This might have been due to diminished transmitter release, although the finding in the frog sciatic nerve of reduction of the amplitude of CAP with high frequency stimulation upon application of local anesthetics (20,21) suggests that an alternative explanation is plausible as well.

The relevance of our findings to the clinical practice of anesthesia is worth discussing. During epidural anesthesia with lidocaine or bupivacaine, some amount of the drugs may diffuse out toward the paravertebral sympathetic ganglia where they block the ganglion cells, thus prolonging the duration of chemical sympathetic denervation. It is possible that while there is regression of epidural anesthesia, reflected clinically as recovery of motor and sensory functions, the sympathetic system may still remain depressed, and thus unable to provide compensatory responses to, for example, orthostatic changes in blood pressure. If so, it is prudent to advise patients against standing immediately after motor and sensory blockade has disappeared. This is especially important in old and/or debilitated patients with borderline or diminished cardiovascular reserve, where cardiovascular regulatory and compensatory mechanisms are in a compromised state.

During spinal anesthesia, while block of the sympathetic fibers occurs within the subarachnoid space, if the local anesthetics diffuse through the spinal gray matter (as opioids do) to reach the sympathetic preganglionic cells in the lateral horn, a prolonged depression of the sympathetic efferent system may be expected, and the same considerations expressed above during epidural anesthesia would apply.

During lumbar sympathetic block where all components of the lumbar sympathetic synapses, namely the pre- and postsynaptic parts, get exposed to the local anesthetic, it may well be that the duration of the lumbar sympathetic denervation will be determined by the duration of the postsynaptic cell block, rather than by the duration of the sympathetic fiber block. Likewise, during celiac plexus block, by virtue of the fact that the local anesthetic diffuses to the celiac ganglion and causes ganglion cell block, the local anesthetic-induced ganglion cell block may be the determining factor for the duration of blockade of sympathetic efferent impulses to the target organs rather than the local anesthetic-induced sympathetic fiber block.

The local anesthetic potentiation of high-frequency ganglionic blockade implies that when a volley of high-frequency efferent sympathetic impulses are generated to increase the blood pressure, the heart rate, or the blood glucose (e.g., in hypotension, bradycardia, hypoglycemia), there will be significant blockade of these efferent impulses at the sympathetic ganglia in the presence of partial synaptic blockade secondary to local anesthetics. Although this is an undesirable pharmacodynamic effect during hypotension or bradycardia, it is a useful phenomenon in patients with autonomic hyperreflexia where severe intraoperative hypertension may occur reflexly if the reflex arc is not blocked by regional or general anesthesia. Obviously when there is complete sympathetic synaptic blockade due to local anesthetics, there will be no synaptic transmission at all, whether the presynaptic impulses are of low frequency or of high frequency.

Is it possible to make any inferences about differential nerve block from the data presented? The effects of lidocaine and bupivacaine were studied on sympathetic synaptic components, namely the pre- and postganglionic components. Our results clearly demonstrate that the sympathetic postsynaptic cell is more sensitive to the depressant effects of lidocaine and bupivacaine than the presynaptic components (B fibers). Although we did not study the effects of lidocaine and bupivacaine on somatic motor and sensory nerve fibers (A and C fibers), based on our present knowledge of the differential sensitivity of the nerve fibers (A, B, and C) to local anesthetics, it is reasonable to assume that the sympathetic postsynaptic cell is the most sensitive to local anesthetics relative to that of the nerve fibers.

The potency and duration of action of bupivacaine relative to those of lidocaine in our preparation are in general agreement with the clinical observations that, in equal amounts, bupivacaine is four times more potent than lidocaine (22), and has a duration of action three times longer than that of lidocaine (23).

Our methodology allowed simultaneous monitoring of the postsynaptic cell EPSP and AP evoked by preganglionic nerve stimulation, of postsynaptic cell AP elicited by direct cell stimulation, and of postganglionic CAP in response to preganglionic nerve stimulation. This arrangement permitted a realization of the temporal relation of the events on application of the anesthetics. The present experimental model can also be used to study interactions among anesthetics and neurotransmitters, neuromodulators, and other synaptically active drugs.

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Fundamental Properties of Local Anesthetics. II. Measured Octanol:Buffer Partition Coefficients and pK_a Values of Clinically Used Drugs

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STRICHARTZ GR, SANCHEZ V, ARTHUR GR, CHAFETZ R, MARTIN D. Fundamental properties of local anesthetics. II. Measured octanol:buffer partition coefficients and pK_a values of clinically used drugs. Anesth Analg 1990;71:158–70.

Because local anesthetic molecules interact with ion channel proteins embedded in membranes to effect impulse blockade, and because their clinical potency often depends on both vascular absorption and distribution into the tissue surrounding the site of deposition, the ability to partition into these various compartments is an important determinant of local anesthetic action. Therefore, the hydrophobic nature of local anesthetics used clinically was characterized by the octanol:buffer partition coefficients of their charged (P^+) and neutral (P^0) species. This was accomplished by previously described optical methods in which direct spectrophotometric measurement of both the pH-dependent distribution coefficient (Q) and of the ionization permit calculation of the pK_a and partition coefficients. The rates of alkaline hydrolysis of ester-linked molecules also were measured to assess potential interference of such hydrolysis with the physicochemical assays. Results indicate that the hydrophobicity of a local anesthetic is increased by manipulation of the molecular structure at three sites: (a) the aromatic ring; (b) the intermediate linking group; and (c) the tertiary amine. P^0 for the agents studied was 10^3–10^5 times greater than P^+. Although there is no systematic relationship between hydrophobicity and pK_a, the latter is greater with ester-linked (pK_a = 8.59–9.30) than with amide-linked (pK_a = 7.92–8.21) local anesthetics. All of the charged species, with the exception of bupivacaine, selectively partition into the aqueous environment ($P^+ < 1.0$). The temperature dependence of partitioning of the local anesthetics, measured at 25 and 36°C, indicates an entropy-driven hydrophobic uptake. Solutions buffered with bicarbonate and including 5% CO_2 showed the same local anesthetic partitioning as that of CO_2-free solutions, suggesting that potentiation of impulse blockade by CO_2 is not due to increased membrane uptake. Correlations of physicochemical properties of local anesthetics with potencies on isolated nerve confirm that the more potent local anesthetics have greater octanol:buffer partition coefficients, and that the ester-linked local anesthetics are more potent than their amide-linked counterparts having the same hydrophobicities. The correlations of structure with potency also suggest that the extracellular protonated species may contribute to impulse blockade.

Key Words: ANESTHETICS, LOCAL—partition coefficients. SOLUBILITY, PARTITION COEFFICIENTS—local anesthetics.

Local anesthetics (LAs), like many neuroactive drugs, must penetrate into or across the neuronal plasmalemma to be pharmacologically active (1–6). Furthermore, in clinical regional anesthetic procedures, the drugs must also traverse the ensheathing perineurium, which is composed of fibrous and cellular barriers, before reaching the nerve fibers (7,8). Thus, membrane permeation and adsorption processes control the LA penetration to and concentration at the site of action. Because the nonprotonated, electrically neutral base of tertiary amine LAs is more membrane-permeant than the protonated, charged form, it accounts for most of the bulk passage of drug through membrane hydrophobic barriers (5,9). Before we can understand the chemistry of these processes in membranes we must characterize the behavior in simpler systems. Modeling of these phenomena begins then,

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with the quantitative analysis of hydrophobicity and protonation in simple, two-phase systems.

The distribution coefficient (Q), defined as the ratio at equilibrium of the concentration of drug in some organic phase to the concentration of drug in an aqueous phase, has been used to quantitate the degree of hydrophobic partitioning. The influence of hydrophobicity, often characterized by this distribution coefficient, on the diffusion of drugs into cell membranes has an important bearing on biologic actions. Indeed, several direct systematic relationships between LA potency and hydrophobicity have been reported previously (5,10–12), providing evidence for the concept that drug interaction with hydrophobic domains of membranes or their associated proteins is a prerequisite for expression of their pharmacologic activity. This belief has allowed partition coefficients of LAs to serve as one criterion in describing their sites of action.

Unfortunately, the available literature lists distribution coefficients of LAs that are often from poorly controlled studies, either using unbuffered solutions or not maintaining ionic strength, or are derived from theoretical considerations (11,13). Previous work lacks uniformity for many drugs with regard to the solvent systems (e.g., olive oil, mineral oil, heptane, or octanol have all been used as the nonpolar phase), temperature, ionic strength, and buffer capacity. Other studies, performed using strongly alkaline aqueous phases, assume that the only meaningful measurement is that of the un-ionized, neutral form of the drug. However, the strong evidence that amine LAs exert their effects to a large degree when present as the charged (protonated) species in excitable membranes (4,5,14) requires a consideration of the intramembranous distribution of cationic molecules as well as neutral ones.

In this study, we measured distribution coefficients (Q) and pK_a values and from these calculated partition coefficients of the neutral and charged species (P^0 and P^+, respectively) of commonly used LAs (LAs: Figure 1) in an octanol:buffer system. Defined as the ratio, at equilibrium, of the concentration of the individual species (neutral or charged) in the organic solvent to the concentration in the aqueous phase, these coefficients may provide information on the species that contribute to drug-membrane interactions. We also wished to meet two other objectives: (a) to recognize partitioning patterns in relationship to the three different structural "zones" of LA molecules; and (b) to provide baseline partition coefficient data for past and future structure-activity analyses.

In addition, concern about the potential hydrolysis of ester-linked LAs in the alkaline solutions used for pK_a measurements led to direct assays of these reaction rates in acid and alkaline solutions at room temperature and 37°C.

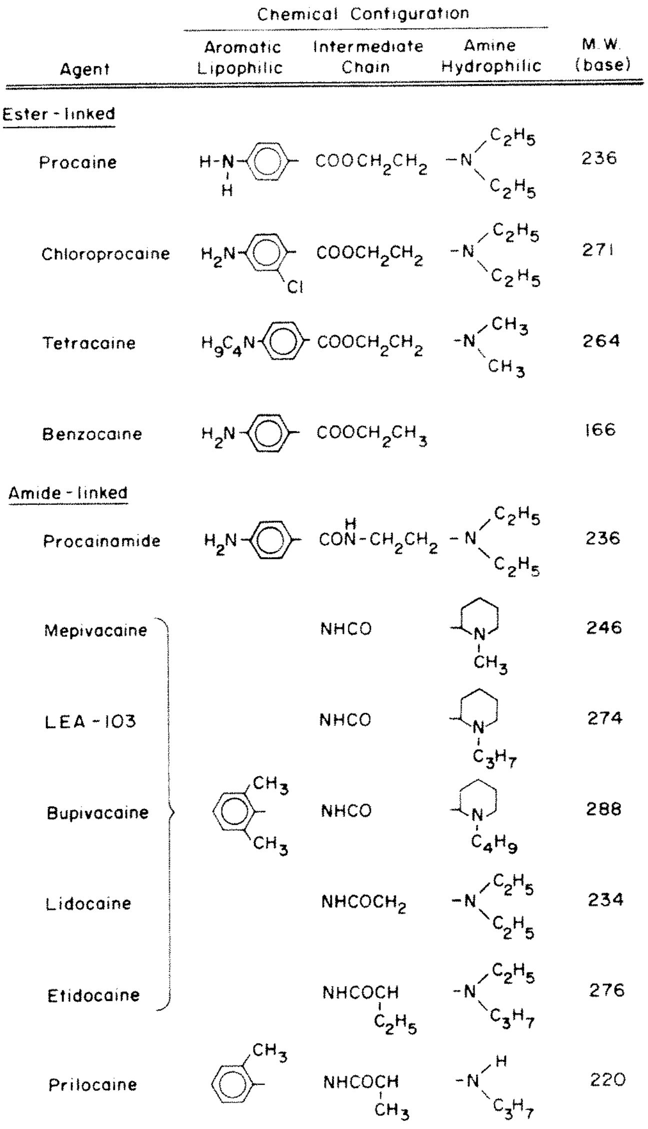

Figure 1. Structures and molecular weights (base) of three amino-ester and seven amino-amide local anesthetics, plus benzocaine, an ester lacking the tertiary amine.

Methods

Determination of pK_a

A modification of the spectrophotometric method (15) described by Albert and Serjeant (16) was used to measure the stoichiometric pK_a of the LAs. A buffered standard aqueous solution (SAM, see Reagents and Solutions) saturated with octanol was used in these studies and contained the following concentrations of local' anesthetic: procaine, 0.5 mM; 2-chloroprocaine, 0.5 mM; tetracaine, 0.5 mM; lidocaine, 10 mM; mepivacaine, 10 mM; LEA-103 (ropivacaine), 5 mM; bupivacaine, 1 mM; etidocaine, 1 mM; prilocaine, 10 mM

The solution was adjusted to either pH 4 or pH 11 using 1 N HCl or 1 N NaOH, respectively. The analytical wavelengths used were generally those of maximum absorbance, as follows: procaine, 247 nm; chloroprocaine, 252 nm; tetracaine, 250 nm; lidocaine, 271 nm; mepivacaine, 271 nm; LEA-103 (ropivacaine), 271 nm; bupivacaine, 271 nm; etidocaine, 272 nm; prilocaine, 262 nm. The absorbance at pH 4 was designated as A_I, the absorbance at pH 11 as A_N. A series of absorbances (A_S) measured at intermediate pH values was then used in a modified Henderson–Hasselbalch equation for determination of the pK_a (16), which was assessed at two different temperatures, 25 and 36°C.

The pK_a values were also determined potentiometrically, using a glass-silver chloride combination electrode (model 13-620-281; Fisher Scientific, Fairlawn, N.J.) coupled to a high-impedance, digital pH meter (Corning Instruments, model 1011). The method described previously in Sanchez et al. (15) and adapted from Albert and Serjeant (16) was employed, using standard buffers (Fisher Scientific, Woburn, Mass.) to calibrate the pH meter from pH 4 to pH 11, and titrating LA solutions with 0.1 N NaOH (made from dessicated NaOH pellets) and 0.1 N HCl diluted from a concentrated stock solution.

Determination of Q Values

The distribution coefficients, Q, were determined spectrophotometrically and, to validate further this technique, were confirmed by gas chromatographic measurements for lidocaine, mepivacaine, prilocaine, and bupivacaine. Data from both methods were found to be consistent.

The procedure closely followed one reported previously from this laboratory (7). Ten millimolar of the local anesthetic (L) was constituted in 25 mL *standard aqueous medium* (SAM, see solutions, below) previously saturated with octanol at low pH and the total anesthetic concentration, $[\bar{L}]$, was measured. An equal volume of octanol (previously equilibrated with SAM) was mixed with the aqueous solution for 5 min and the phases allowed to separate vertically for 15 min. The pH of the aqueous phase was then measured. After the removal of 1-mL samples from each phase, the local anesthetic concentration of only the aqueous phase, $[L]_{aq}$, was measured. The Q value was then calculated using the following equation:

$$Q = \frac{[\bar{L}] - [L]_{aq}}{[L]_{aq}}, \tag{1}$$

where the numerator is the amount of drug that had been extracted into the octanol.

The aqueous-octanol mixture was titrated progressively with 1.0 N NaOH and Q values were determined at different pH values, never exceeding pH 8.0 and rarely greater than pH 6.0. Relatively low pH values were used to maintain a measurable amount of drug as the protonated form that tends to partition in the aqueous phase. These data were subsequently used to calculate P^0 and P^+ (see below and Reference 15). In one set of experiments, the pH was reacidified from 6 to 4 with 6.0 N HCl, with no difference between the initial and final Q values measured at the lower pH, indicating that irreversible changes that could affect this parameter did not occur during the normal titration procedure. Distribution coefficients were determined at two different temperatures, 25 and 36°C.

Calculation of Partition Coefficient

The data obtained were further analyzed to derive partition coefficients for the neutral (P^0) and charged (P^+) species by a linearized function (Equation [2]) relating Q to the extent of ionization, β ($= 10^{pK_a - pH}$):

$$(1 + \beta)Q = \beta P^+ + P^0. \tag{2}$$

The validity of this method has been established previously for lidocaine (15).

Hydrolysis

Rates of alkaline hydrolysis were assessed spectrophotometrically at pH ≥ 11.0. Solutions of ester-linked LAs in SAM were incubated in a water bath at 37°C or room temperature (22–25°C), and aliquots were periodically withdrawn until the reaction was complete. Hydrolysis was interrupted either by addition of 1 N HCl to acidify the sample (pH < 6) followed by cooling on ice, or by rapid freezing (<10 min to freeze completely) at −80°C. The calculated rates of hydrolysis were independent of the quenching method.

The difference between the temperature used for hydrolysis reactions (37°C) and that used for the equilibrium measurements (36°C) was unintentional and became apparent only after we used the same thermometer to measure the temperatures under experimental conditions. We doubt that the 1°C difference significantly affected the results or conclusions.

For all the LAs, the selected ultraviolet absorbance decreased almost to zero upon hydrolysis, except for 2-chloroprocaine, which showed an increase in absorbance (see Results). Wavelengths used for each LA were (nm): benzocaine, 288.5; procaine, 296; 2-chloroprocaine, 252; tetracaine, 315; and lidocaine, 271 nm. In one control experiment, lidocaine was incubated in SAM at pH 11 and 37°C for 8 h; its absorbance did not change significantly, confirming the relative stability of amide-linked LAs.

The normalized change in absorbance was plotted semilogarithmically against time (cf. Figure 2B) and the slopes of lines fit to these data by linear regression were equated with the relative rate constants. Absorbance changes of LA incubated in acidic solutions were used as internal controls.

Reagents and Solution

Reagents. All amide-linked local anesthetics and 2-chloroprocaine were gifts from Astra Pharmaceutical Corporation (Worcester, Mass.). All LAs containing asymmetric carbons (e.g., mepivacaine, bupivacaine) occurred as the racemic mixture, with the exception of ropivacaine, which was present only as the S-(-) isomer (LEA-103). Tetracaine and procaine were purchased from Sigma Chemical, St. Louis, Mo., and benzocaine from Aldrich Chemicals, Milwaukee, Wis. Buffers were from Calbiochem-Boehring, La Jolla, Calif. 1-Octanol (ACS certified 99.93%) and NaCl were obtained from Fisher Scientific Company (Fairlawn, N.J.).

Solutions. The standard aqueous medium (SAM) consisted of 150 mM NaCl, 5 mM 2-(*N*-morpholino) ethanesulfonic acid, 5 mM morpholino-propane sulfonic acid, and 5 mM (3-cyclohexylamino)-propane sulfonic acid in water. Together these buffers provided a relatively constant buffering capacity from pH 5 to pH 11. Deionized water was saturated with octanol by mixing 25 mL of SAM and 1 mL of octanol for 10 min, then centrifuging the mixture at 900 *g* for 20 min to separate the organic and aqueous phases. This procedure was performed at the same temperature at which experimental measures of pK_a and Q were to be made. The octanol used for the determination of Q and pK_a values was saturated with SAM using the same technique. The aqueous media used in the determination of pK_a values were also saturated with octanol unless otherwise stated.

Spectrophotometry. Absorbances of anesthetic solutions were measured with a Gilford Response UV-Vis Spectrophotometer (Gilford Instrument Laboratories, Inc., Overton, Calif.). Ultraviolet absorbance spectra of the LAs in SAM saturated with octanol were performed using matched quartz cuvettes. Sealed solutions were incubated for a minimum period of 18 h before spectrophotometric measurements of Q in order to ensure equilibrium and permit the escape of any microscopic bubbles. Control aqueous solutions of LA without octanol were of constant ultraviolet absorbance (±3%) over this time.

Incubations of solutions for both pK_a and Q values were performed using a double-walled, temperature-controlled, 50-mL Reacti-Vial from Pierce Chemical Co. (Rockford, Ill.) with an internal magnetic stirrer. Temperature was maintained using a water heating circulator (B. Brown Thermomix, model 1420) and measured by a model 42 SC Tele-Thermometer (Yellow Springs Instruments, Yellow Springs, Ohio).

Results

Valid measurement of pK_a must be predicated on the stability of the compounds throughout the range of titration. Therefore, the well-known alkaline hydrolysis of ester-linked local anesthetics (17) was assayed at room temperature and 37°C. The time-dependent absorbance decrease of an alkaline solution (pH 11.4) of tetracaine at 37°C is graphed in Figure 2A, and the semilogarithmic plot of the normalized absorbance change is presented in Figure 2B. The good fit to a straight line confirms the exponential behavior of this reaction and from its slope a rate constant for alkaline hydrolysis, k_{hyd}, is calculated. Values of k_{hyd} for four ester-linked LAs are collected in Table 1.

Hydrolysis is fastest for 2-chloroprocaine, slowest for benzocaine and tetracaine. For all four compounds, hydrolysis is about four times faster at 37°C than at room temperature. The shortest half-time that corresponds to these rate constants, that for 2-chloroprocaine, is about 40 min. Thus, during titration measurements, the time that a 2-chloroprocaine solution was at pH 11 or above, 10 min at most, allowed 16% of the LA molecules to be hydrolyzed. Because hydrolysis of 2-chloroprocaine leads to an increase in optical absorbance at 252 nm, which is the same effect as acidification (ionization) in the absence of hydrolysis, the potential artifactual result of hydrolysis leads to a pK_a higher than the true one. The

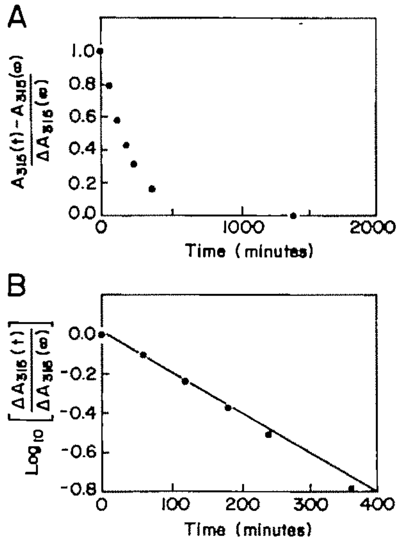

Figure 2. Hydrolysis of tetracaine. A solution of 10^{-4} M tetracaine in SAM was warmed to 37°C and the pH rapidly raised from 5.6 to 11.4 by addition of 1 N NaOH at "zero" time. Aliquots were removed at the times noted, and the absorbance of the solution at 315 nm (A_{315}) was measured spectrophotometrically. The total change in absorbance after complete hydrolysis ($\Delta A_{315}(\infty)$) was divided into the difference between A_{315} at a specified time ($A_{315}(t)$) and the final absorbance ($A_{315}(\infty)$) and plotted against time on a linear scale (A) or semilogarithmically (B). Data in B are fit, using linear regression (least-squares) analysis, by the function $y = 1.85 \times 10^{-2} - 2.2 \times 10^{-3}t$ ($r^2 = 0.998$). The slope of the line gives the hydrolysis rate constant:

$$k_{hyd} = \text{slope} \div \log_{10} = 2.30 \times \text{slope}.$$

Table 1. Rate Constants for Alkaline Hydrolysis of Ester-Linked Local Anesthetics

Drug	k_{hyd} (min^{-1})			
	22–25°C	n	37°C	n
Procaine	$1.96 \pm 0.02 \times 10^{-3}$	3	$8.68 \pm 0.33 \times 10^{-3}$	4
2-Chloroprocaine	$3.55, 5.66 \times 10^{-3}$	2	$1.78, 1.58 \times 10^{-2}$	2
Benzocaine	$9.76 \pm 1.37 \times 10^{-4}$	3	$4.62 \pm 0.22 \times 10^{-3}$	3
Tetracaine	$1.14 \pm 0.04 \times 10^{-3}$	3	$4.76 \pm 0.18 \times 10^{-3}$	3

k_{hyd}, alkaline hydrolysis rate constant.
Values are mean ± SE, except for 2-chloroprocaine, where only the two listed measurements were made.
pH = 11.3–11.4 in standard aqueous medium, adjusted with NaOH.

estimated error would be approximately +0.2 pH units. For all the other LAs, the absorbance at the measuring wavelength was decreased by hydrolysis, artifactually mimicking alkalinization. We estimate that the next largest error in estimated pK_a would occur with procaine, equal approximately to −0.1 pH unit.

(The hydrolysis of the LAs leads to a decreased spectral height and a shift to shorter wavelengths. For most of the drugs that we studied we chose a monitoring wavelength at the absorbance maximum of the intact LA, but for 2-chloroprocaine we used the absorbance maximum of the hydrolysis product because the change in absorbance was greater there. That is why the absorbance [at 252 nm] of the 2-chloroprocaine solution increased with hydrolysis whereas the absorbances of the other LAs [e.g., procaine's at 296 nm] decreased with hydrolysis.)

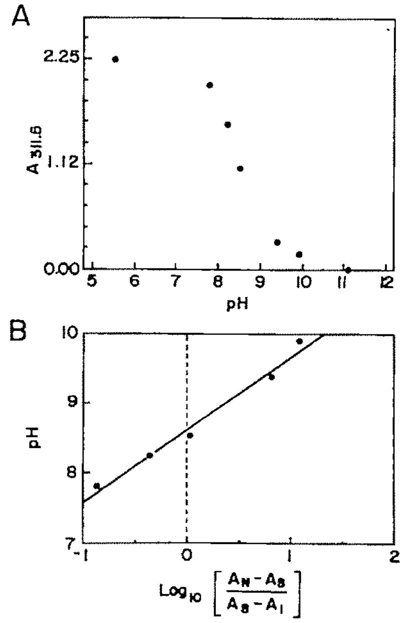

Figure 3. Titration of tetracaine. The ultraviolet absorbance at 311.5 nm was measured at 25°C in SAM at pH values beginning at 5.6 and ending at 11.2 during the incremental addition of 1 N NaOH. The discrete values of $A_{311.5}$ are plotted in A, and a linearized version of these data is regraphed in B (see Methods). A line, fit to the points by linear regression, is described by $y = 8.64 + 1.05x$ ($r^2 = 0.98$), with slope and y-intercept corresponding to a protonation stoichiometry of one H^+ and $pK_a = 8.64$, respectively.

In control solutions, where the LAs where incubated at pH 5–6 and 37°C for 24 h, the absorbances changed by less than 2.5%. Comparison to the absorbance decreases that accompanied complete hydrolysis at pH >11, 50%–70%, shows that acid hydrolysis occurred, at most, at only 5% of the rate of alkaline hydrolysis.

pK_a values for the LAs were determined by a spectrophotometric method, which was often further confirmed by potentiometric means conducted in the same NaCl concentration but without buffers. Data for the titration of tetracaine are shown in Figure 3 as an example. The absolute change in absorbance with pH is plotted in Figure 3A, and the logarithm of the normalized absorbance is plotted in Figure 3B. A straight line with a slope near unity and a value of $y = 8.63$ at $x = 0$ fits the data well, providing respective information on the number of protons (one) participating in the absorbance change (titra-

Table 2. Ionization Constants of Local Anesthetics From Spectrophotometric Method[a]

Drug	Temperature (°C)	pK_a[a]	Samples (*n*)
Ester-linked			
Procaine	25	9.06 ± 0.10	3
	36	8.89 ± 0.08	3
2-Chloroprocaine	25	9.30 ± 0.08	3
	36	9.06 ± 0.05	3
Tetracaine	25	8.59 ± 0.04	3
	36	8.38 ± 0.03	3
Amide-linked			
Procainamide	25	9.42 ± 0.04	3
Mepivacaine	25	7.92 ± 0.03	3
	36	7.72 ± 0.06	3
LEA-103	25	8.16 ± 0.02	3
(Ropivacaine)	36		ND
Bupivacaine	25	8.21 ± 0.04	3
	36	8.10 ± 0.02	3
Lidocaine	25	8.19 ± 0.03	12
	36	7.77 ± 0.04	8
Prilocaine	25	8.02 ± 0.05	3
	36		ND
Etidocaine	25	8.11 ± 0.02	3
	36	7.87 ± 0.03	3

[a] 150 mEq/L NaCl, 5 mM 2-(*N*-morpholino)ethanesulfonic acid, 5 mM morpholino-propane sulfonic acid, 5 mM (3-cyclohexlamino)-propane sulfonic acid.

ND, not determined.

Table 3. Ionization Constants of Local Anesthetics From Potentiometric Method

Drug	pK_a[a]	*n*
Procaine	9.31 ± 0.05	3
2-Chloroprocaine	9.49 ± 0.06	3
Tetracaine	8.59 ± 0.04	3
Mepivacaine	7.92 ± 0.03	3
LEA-103	8.16 ± 0.04	3
Bupivacaine	8.21 ± 0.03	3
Lidocaine	8.05 ± 0.03	12
Prilocaine	8.03 ± 0.04	3

[a] In 0.17 M NaCl at 25°C, with no added buffers.

tion) and on the pK_a. Collected data on the pK_a of tetracaine and of nine other local anesthetics determined spectrophotometrically are listed in Table 2.

When selected local anesthetics were titrated potentiometrically in 0.17 M NaCl solutions lacking any added buffer, the pK_a values were within 0.2 ± 0.1 pH units, and more often within 0.1 ± 0.05 pH units of the values determined optically (Table 3). These values also agree within 0.2 pH units (except for 2-chloroprocaine, the value of which differs by 0.52 pH units) with those measured potentiometrically for six of the same LAs by Kamaya et al. (18), who used

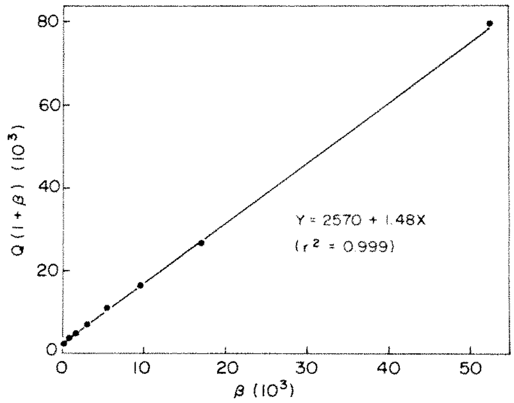

Figure 4. Partition coefficients for bupivacaine (5.1 mM nominal aqueous concentration) between octanol and SAM are derived from the pH-dependent change in the distribution coefficient Q (see Methods). The absorbance at 271 nm of the aqueous phase was monitored for pH values ranging from 3.51 to 5.74; the corresponding A_{271} fell from 2.19 to 0.620. Calculated Q values for these end points were 1.53 and 7.94, respectively (see Equation [1], Methods). When these data are expressed as Equation (2) (see Methods) the plot of this figure results, with slope = P^+ and *y*-intercept = P^0. The equation fits these data extraordinarily well, as noted by the high correlation coefficient for the linear regression analysis.

a lower ionic strength (0.05 M KCl) to minimize deviations from unity of the activity coefficients of H^+. This confirms the validity of the spectrophotometric method, which has the advantage of measuring the pH in the most physiologically relevant solution, one that contains buffers and the LA at the concentration used pharmacologically.

Partition coefficients were calculated from the pH-dependent variation in the measured octanol:buffer distribution coefficient, Q, as described in Methods. One of the best examples of such a calculation is shown by Figure 4, wherein a graphical analysis of partitioning according to Equation (2) is used to determine P^0 and P^+ for bupivacaine. As for most of the LAs, the neutral species partitions into octanol so much more than the protonated species ($\sim 2 \times 10^3$:1 in this case), that values of Q less than 10 are achieved only at very acid pH, where relatively little of the neutral species exists. For example, in the case of bupivacaine shown here, all measurements were made between pH 3.5 and 5.8 to prevent more than 95% of the LA from going into the octanol.

Values of pK_a, P^+, and P^0, and the calculated Q at pH 7.4 are collected in Table 4 for four ester-linked and seven amide-linked local anesthetics.

For many of the compounds tested, parameters are listed at both 25°C and 36°C. In all cases, the pK_a is reduced by cooling, confirming earlier studies of ionization in several local anesthetics (18). The reduction in temperature also was accompanied by a de-

Table 4. Octanol/Buffer[a] Partition Coefficients and Distribution Coefficient at pH 7.4 of Local Anesthetics

Drug	Temperature (°C)	Samples (n)	$P^{+\,b}$	$P^{0\,b}$	$Q_{7.4}{}^{c}$	P^0/P^+ ($\times 10^{-3}$)[d]
Ester-linked						
Procaine	25	3	0.002 ± 0.001	81 ± 6	1.7	40.5
	36	3	0.004 ± 0.01	100 ± 10	3.1	25.0
2-Chloroprocaine	25	3	0.026 ± 0.006	720 ± 63	9.0	27.7
	36	3	0.042 ± 0.010	810 ± 58	17.4	19.3
Tetracaine	25	3	0.46 ± 0.03	3615 ± 294	221.0	7.86
	36	3	0.79 ± 0.05	5822 ± 325	541.0	7.37
Benzocaine	25	3	NA	81	81	NA
	36	3	NA	132	132	NA
Amide-linked						
Procainamide	25	3	0.0021 ± 0.0005	7.3 ± 0.1	0.07	3.5
Mepivacaine	25	3	0.09 ± 0.01	90 ± 11	21.0	1.0
	36	3	0.15 ± 0.05	130 ± 15	42.0	0.86
LEA-103	25	3	0.46 ± 0.03	775 ± 53	115.0	1.7
(Ropivacaine)	36		ND	ND	ND	ND
Bupivacaine	25	3	1.5 ± 0.03	2565 ± 218	346.0	1.7
	36	3	2.0 ± 0.05	3420 ± 263	560.0	1.7
Lidocaine	25	12	0.060 ± 0.005	304 ± 23	43.0	5.1
	36	8	0.085 ± 0.01	366 ± 31	110.0	4.3
Prilocaine	25	3	0.30 ± 0.02	129 ± 11	25.0	0.43
	36		ND	ND	ND	ND
Etidocaine	25	3	0.48 ± 0.03	4900 ± 386	800.0	10.2
	36	3	0.81 ± 0.05	7317 ± 523	1853.0	9.0

NA, not applicable; ND, not determined.

[a] 150 mEq/L NaCl, 5 mM 2-(*N*-morpholino)ethanesulfonic acid, 5 mM morpholino-propane sulfonic acid, 5 mM (3-cyclohexylamino)-propane sulfonic acid.

[b] Partition coefficients expressed as relative concentrations (mol/L) in octanol and buffer.

[c] $Q_{7.4}$ equals (total drug/mL octanol) + (total drug/mL buffer) at pH 7.4.

[d] P^0, P^+: ratio of the relative concentrations (mol/L) of protonated and neutral drug, respectively, between octanol and buffer.

crease in the partition coefficients; for the charged species (P^+) this decrease ranged from 25% to 50%, whereas it was consistently less for the neutral species (P^0). The overall effect of cooling was to lower the total amount of LA that distributed into the octanol phase, as seen by the changes in $Q_{7.4}$ values listed in Table 4.

We also investigated the effect of CO_2-bicarbonate on the distribution of LAs between octanol and aqueous media. Using a modified solution of SAM, where 5 mM of NaCl was replaced by an equal concentration of $NaHCO_3$, we bubbled CO_2 through the aqueous phase at different flow rates to yield steady-state pH values ranging from 4 to 6.5. After 8 h of this equilibration, samples were taken from both phases and the measured distribution coefficients used to determine the octanol:buffer partition coefficients. As shown in Table 5, neither P^+ nor P^0 was altered significantly by the presence of this modest concentration of bicarbonate. Table 5 also lists results for lidocaine and tetracaine that demonstrate the independence of the partition coefficients from the LA concentration.

Table 5. Effect of Local Anesthetic Concentration and of CO_2 on Octanol: Buffer Partition Coefficients[a]

Drug	[LA][b]	P^+	P^0	n
Lidocaine/SAM	15 mM	0.51	2,584	12
Lidocaine/SAM	100 mM	0.60	2,508	2
Lidocaine/5 mM HCO_3^-:CO_2[c]	15 mM	0.42	2,635	2
Tetracaine/SAM	0.5 μM	3.91	30,730	3
Tetracaine/SAM	40 μM	3.66	30,702	1

LA, local anesthetic; SAM, standard aqueous medium.

[a] All measurements at 25°C.

[b] Nominal aqueous concentration.

[c] Fifteen millimolar added bicarbonate plus CO_2 gas at flow rates to adjust pH to values from 4 to 6.5 in 170 mM NaCl.

In an effort to see whether organic acids that are more hydrophobic than CO_2 could alter the octanol uptake of LA, we examined the distribution coefficient of procaine between octanol and SAM, to which was added increasing amounts of *n*-alkyl carboxylic acids. The results (Figure 5) show that the distribution into octanol of procaine is influenced by carboxylic acids, with those of longer alkyl length being

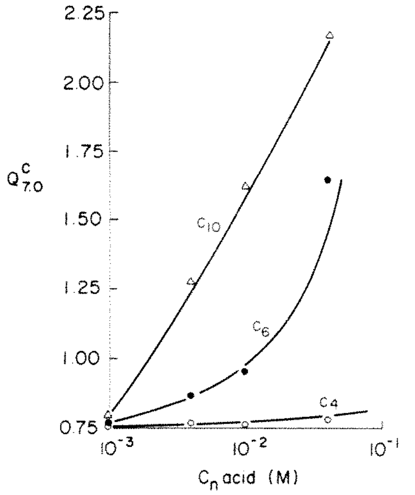

Figure 5. The octanol:buffer distribution coefficient of procaine, at pH 7.0, 25°C (as a ratio of concentrations), is plotted against the nominal aqueous concentration of *n*-alkyl carboxylic acid. C_4 = butyric acid; C_6 = hexanoic acid; C_{10} = decanoic acid.

more effective. Under these conditions, procaine in the aqueous phase is highly ionized (99.1%: see Table 2), but the partition coefficients are in the ratio $P^0:P^+ = 4 \times 10^4$ so the net distribution is dominated by the uptake of the neutral species, in the ratio of 320:1 over the charged form. In order to double the Q, therefore, either the partition coefficient of the neutral species would need to double, or that of the charged form would need to increase 320-fold, or, as a third possibility, the effective pK$_a$ would have to decrease by at least 2 pH units.

Discussion

The results of this investigation provide data for analyzing the structural basis of physicochemical properties of LAs, for comparing the measured hydrophobicity values with calculated values reported previously, and for refining structure-activity relationships for pharmacologic actions of LAs. We will address these points in the following.

Rates of Hydrolysis

Our calculated pK$_a$ values were affected at 37°C only slightly by the alkaline hydrolysis that cleaves ester-linked LAs, and were affected not at all at room temperature. The hydrolysis rates of ester-linked LAs measured in SAM were far slower at neutral pH than at alkaline values, reproducing observations of 2-chloroprocaine and procaine hydrolysis in buffered cerebrospinal fluid made 38 yr ago (17). However, even at pH 11 in buffer alone, the hydrolysis rate of 2-chloroprocaine is only 2% of its enzymatically catalyzed rate in serum; that of procaine is 8% of its enzymatic rate (19).

Structural Basis of Physicochemical Properties

Partition coefficients of clinically useful local anesthetics vary considerably depending on the number and types of substituents on the aromatic ring, the type of bond in the intermediate chain, and the addition of alkyl groups attached to the amine nitrogen. Obviously, the value of pK$_a$ also contributes significantly to the distribution coefficient at pH 7.4.

Variations in substituents on the aromatic group and on the tertiary nitrogen affect both hydrophobicity and pK$_a$. The addition of chloride to the 2-position of the amino-benzoate ring in procaine to yield 2-chloroprocaine increases the partitioning of both the neutral and protonated species about eightfold, and also results in a 0.17 unit increase in the pK$_a$. Together these functions effect a fivefold increase in the physiologically pertinent distribution coefficient (pH 7.4, 36°C).

By comparison, the octanol:buffer partitioning of tetracaine, which has a butyl group bound to the para-amino nitrogen, is 40–50 times that of procaine, even though the presence of methyl groups on the tertiary amine of tetracaine, in lieu of the ethyl groups in procaine, results in a net structural difference of only two additional methylene moieties in tetracaine. A parallel comparison can be made between mepivacaine and LEA-103 (S-(-)ropivacaine); the latter differs from mepivacaine only by the addition of an ethylene (2 carbon) moiety on the tertiary amine nitrogen, and partitions into octanol 5–10 times more than mepivacaine. Analogously, the lidocaine homologues with one ethyl and either a propyl (RAD 241) or pentyl (RAD 242) group on the tertiary amine nitrogen have one and three more methylene ($-CH_2-$) groups than lidocaine, thus differing from each other by two $-CH_2-$ groups. These two compounds differ only 4.5-fold in their P^0 values, and 15-fold in P^+ values (V. Sanchez and G. R. Strichartz, unpublished observations). Comparison of the tetracaine:procaine pair with the behavior of the other pairs of LAs indicates that alkyl substituents at the aromatic end of the LA molecule have a greater influence on partitioning into octanol than do similar substitutions on the tertiary amine.

Still, the addition of alkyl groups to the amine nitrogen increases both partition and distribution coefficients in general. For example, in most of the anesthetics the value of P^0 is 10^3–10^5 times greater than the P^+ value for the same molecule, yet the lowest ratio (430) occurs in prilocaine, which, as a secondary amine, has the fewest alkyl amino groups. Prilocaine has a different electronic structure for the ionizable nitrogen than do the 3° amine LAs, one that permits van der Waals (dipole-dipole) interactions between solvent molecules and the amino nitrogen, even in the protonated form.

The role of amino substitutes is also evident in the mepivacaine series, where a strong positive correlation exists between P values and the length of the alkyl group on the piperidine ring nitrogen. The mepivacaine series exhibits an unusually high P^+:P^0 ratio, as well as large absolute P^+ values (see Table 2). Of all the charged LA species, only bupivacaine selectively partitions into the organic phase ($P^+ > 1$). Even tetracaine and etidocaine, which have P^0 values exceeding that of bupivacaine, have P^+ values less than unity. Molecular models show that the tertiary amine nitrogen in bupivacaine is shielded from solvent molecules by a close-packed hydrophobic shell that may increase the effective radius of the charged group sufficiently to lower the electrostatic work required to move the molecule from water to a low dielectric medium (20). The neutral species of all LAs, in contrast, resides overwhelmingly in the hydrophobic phase ($80 < P^0 < 7000$).

The type of bond in the intermediate chain also influences physicochemical properties. Compared to procaine, procainamide has a 10-fold smaller partition coefficient for both charged and neutral species. The pK_a of procainamide at 25°C is 9.42; that of procaine is 9.06. This same trend occurs between lidocaine and its ester-linked counterpart, RAG 505 (V. Sanchez and G. R. Strichartz, unpublished results). Thus, changes that are effected in drug distribution between bulk solvents are comparable among different molecular pairs where amide bonds are substituted by ester bonds. This holds true independent of the orientation of the bond in the anesthetic molecule, the ester bond in procaine being, for example, directed opposite to that in RAG 505, and, similarly, the amide bond in lidocaine being directed opposite that in procainamide (Figure 1).

The net effect of cooling is to reduce the LA concentration in octanol both by elevating the pK_a and reducing the partition coefficients, P^+ decreasing a bit more than P^0 (Tables 2 and 4). A detailed thermodynamic analysis of ionization and partitioning has been applied to a series of lidocaine homologues (V. Sanchez and G. R. Strichartz, unpublished observations). The conclusion of that analysis is that LAs selectively partition into octanol because the free energy of the system is minimized by a dominant increase in entropy; in other words, the extent of disorder (entropy, ΔS) is maximized when the LA is in the organic phase. The hydrophobic regions of LA molecules tend to order the H_2O molecules when they are present in the aqueous phase. The free energy difference that occurs upon partitioning, ΔG, is the sum of entropic and enthalpic (bond energy) terms:

$$\Delta G = \Delta H - T \cdot \Delta S. \tag{3}$$

Because the values of ΔG for LA partitioning are dominated by the larger $T \cdot \Delta S$ term, changes in temperature effect a major change in P values through this product.

The ability of the different solvents to form bonds with the LA determines ΔH, the enthalpy difference. For example, the likely reason that the ΔH for LA partitioning into hexane is so much greater than that in octanol (21) is because the pure hydrocarbon solvent can form neither the van der Waals bond nor the hydrogen bond of which the alcohol is capable.

The effect of cooling on the physiologic potency of LAs is noteworthy. Decreases in temperature increase the potency of LA markedly; in frog nerve the impulse-blocking actions of lidocaine are increased eightfold upon cooling from 21 to 7°C (G. Strichartz and P. M. Bokesch, unpublished observations). Qualitatively similar results have been reported for the effect of lidocaine in mammalian nerve (22) and for nonionizable local anesthetics in amphibian nerve (23). That the octanol:buffer partitioning decreases as potency increases with decreasing temperature requires that real membranes behave differently than octanol or that drug binding at the site of action has a strong negative temperature dependence, with increasing occupancy in colder nerves (24).

Comparison to Published Physicochemical Properties

The physicochemical values reported in this study bear comparison to those published in previous papers. Many of the cited values of pK_a refer back to industrial measurements (13) and do not include information on the salt concentration of the aqueous medium, the temperature, or the method of measurement, which is most likely potentiometric. We consulted four sources: one recent paper in an anesthesia journal (25), one paper published 7 yr ago in an anesthesia journal (18), one paper from the relatively recent pharmacologic literature (11), and one recently published textbook of local anesthesia (21). The pK_a

values reported in these sources agree moderately well with the ones we measured at 25°C. For example, published values for lidocaine were, respectively, 7.7, 7.91, 7.9, and 7.91 (the last value from Reference 21, which cites Reference 18), ours was 8.2. The reported pK_a values for procaine were 9.0, 9.0, and 9.05, respectively; ours was 9.06. The largest discrepancy in pK_a was for etidocaine; we measured its pK_a as 8.1, whereas a pK_a of 7.7 was listed by three of the sources.

These small differences in pK_a have modest consequences for the calculated degrees of ionization. The largest difference, 0.4 pH units for etidocaine, results in our estimate of this LA being 84% ionized at pH 7.4, whereas the lower pK_a of the other literature would have it only 67% ionized. Obviously, the complementary relationships for the neutral species are 16% and 33%, respectively, a twofold difference in the uncharged fraction. The uncharged molecule is the molecular form traditionally associated with LA acting from outside the nerve membrane, and the factor of 2 in estimating the concentration of the neutral form would affect both the calculated partition coefficient (see Equation [2]) and the apparent potency assigned to this species.

Two of the references cited above (11,25) list octanol:water partition coefficients for neutral (base) LAs calculated from a linear form of substitution analysis (26); one (21) also lists heptane:buffer distribution coefficients at pH 7.4 (temperature and buffer not specified). Comparing these two parameters, in that order, with our own measured values, we found that the calculated values (which differed between themselves, although based on the same theoretical scheme) rarely matched the measured ones. For example, P^0 values given for tetracaine were 5370 and 2511, whereas we measured 3600. Our value of 4900 for etidocaine was much closer to that of 2340 from Reference 25 than to the 24,000 calculated by Reference 11. The discrepancies were usually about a factor of 2, although the P^0 value of bupivacaine was calculated (only in Reference 11) to be 21,400, eight times greater than our measured one. The P^0 value of procaine listed as 210 (25) and 100 (11) was found by us to be 80. As a result of these discrepancies we suggest caution in using octanol:aqueous partition coefficients calculated from semitheoretical schemes (e.g., Reference 26) as the correct values for hydrophobicities.

The distribution coefficients for LAs at pH 7.4 are much greater when octanol is used than when heptane is employed (21). Examples of these respective values are lidocaine (43 with octanol; 2.9 with heptane), procaine (1.7; 0.02), tetracaine (221; 4.1), bupivacaine (346; 27.5), etidocaine (800; 141). These ratios are not unpredicted, because the hydroxyl moiety of octanol can form hydrogen bonds as well as have other energetically favorable interactions with the polar regions of LA molecules, activities in which purely hydrocarbon heptane cannot participate. Similar differences will be reported for a series of lidocaine homologues in a forthcoming paper.

To compare better the distribution coefficients of different LAs between buffer and heptane (21) with those we calculated between buffer and octanol, we related the Q values in each solvent to their respective values for lidocaine. Thus bupivacaine distributes 9.5 times more than lidocaine into heptane (over buffer) and 8.0 times more than lidocaine into octanol. This was the closest agreement we found. The other LAs had higher relative distribution coefficients into octanol than into heptane, with the exception of etidocaine. This last observation is one example of the unusually high hydrophobicity of etidocaine. The bulky alkyl substituents on its amino nitrogen limit the nearness of approach of polar solvent molecules to the amine nitrogen and, perhaps, even to the amide group; they thus reduce the capability of octanol (or water) to stabilize the LA by weak bond formation.

Structure-Potency Relationships for Physiologic Actions

The potency of LAs is generally defined as the dose necessary to achieve a specified end point. Clinically, the potency is usually the total mass (or moles) of drug required to relieve or prevent pain, produce tactile numbness, or effect inhibition of sympathetic or motor activity. Clinical end points are rarely "titrated," however, as a margin of safety for the desired effect is most often necessary, and the potency of local anesthesia is usually assessed by the anatomic extent of the block that is achieved or even by its rate of onset. The relative potencies of LAs in these assays are highly dependent on anatomic and physiologic factors (e.g., body size, posture, vascularity of injection site). But for the fundamental parameters we report here we will attempt correlations of potency with much simpler systems. Our aim is to compare the *concentrations* of LAs in a bathing solution that equilibrates with an isolated nerve to yield a *steady-state effect*. The relative potency defined here is inversely proportional to the effective drug concentration, which is constant during the assay. From such *dose-response* data we can perceive correla-

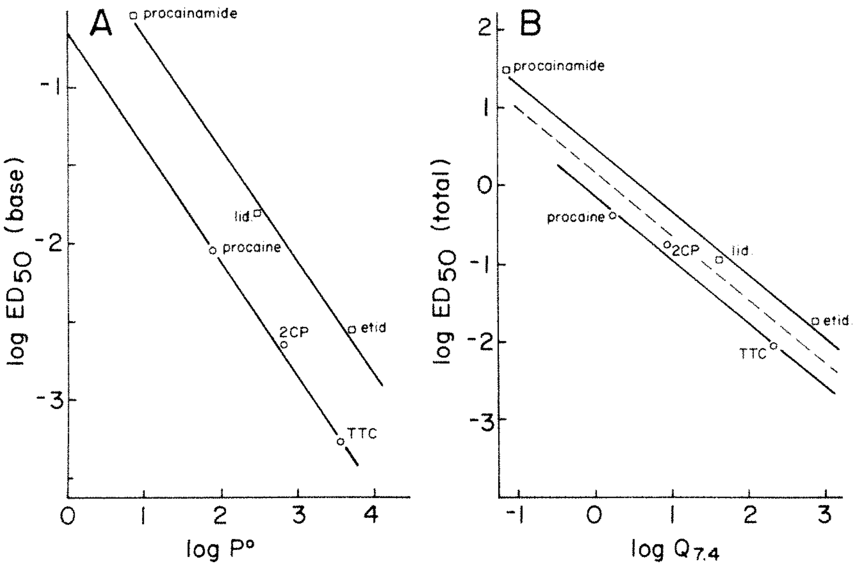

Figure 6. The relationship between LA potency, for inhibition of compound action potentials, of A fibers in rabbit vagus nerve and physicochemical properties. **A**, The calculated concentration of the base (uncharged) species required to halve the action potential, in mM, is plotted against the octanol:buffer partition coefficient for that species, P^0, on a log-log scale. For the three amino-esters (○) the best fitting line is described by $y = 0.643 - 0.730x$ ($r = 0.997$); for the three amino-amides (□) it is $y = 0.036 - 0.714x$ ($r = 0.999$). **B**, If potency is calculated as the total concentration of LA and plotted against the distribution coefficient ($Q_{7.4}$), the lines of the log-log plot are described by $y = -0.118 - 0.815x$ ($r = 0.996$) for amino-esters and $y = 0.499 - 0.812x$ ($r = 0.999$) for amino-amides. Potency values derived from Wildsmith et al. (Reference 25); P^0, pK_a, and $Q_{7.4}$ values from this paper.

tions between apparent potency and physicochemical properties.

Correlations between the structure and the pharmacologic activity of LAs are often made on the assumption that only the neutral species can penetrate the nerve membrane to bind at the site of action. A clear expression of this assumption occurs when potency data are listed by the concentration of the neutral species (base) and compared with some physicochemical property of that form of the LA. In Figure 6A we present such a plot, using previously published experimental results on the impulse-blocking potency of three ester-linked and three amide-linked LAs (25); the values of EC_{50} for the base (the concentration of neutral LA required to halve the peak of the compound action potential, at pH 7.4 and 23°–26°C) and of P^0 have been corrected by, and to, the respective values of pK_a and P^0 reported here.

Several aspects of this plot deserve attention. First, the line fitting the ester-linked LA data is parallel to, and below that of, the line for amide-linked drugs. Thus, the intrinsic potency of the amino-ester compounds appears greater than that of the amino-amide LAs, and both classes change identically as a function of "hydrophobicity." Second, the points are well-fit by the lines, admittedly for only three values in each class, and such strong correlations (of linear regression analysis) are consistent with the assumption of eventual potency conferred through the hydrophobic permeation of the neutral species. All these points were noted by the original authors (25).

Yet a broader view of LA behavior allows that the charged form of the drug adsorbs to membranes, and that protonation at a site of action, i.e., the sodium channel of excitable membranes, can be accomplished by protons in the extracellular medium (27–29). A more ecumenical analysis follows from these admissions and includes consideration of the total concentration of drug in the bathing solution for the potency and of the total distribution (Q) of drug into the membrane at physiologic pH. When the data are plotted on these scales (Figure 6B) they also produce parallel lines with apparent intrinsic potency differences. Yet a single line fits all six data points from both LA classes almost as well as each class is fit on its own ($r = 0.979$ vs $r = 0.997$ and 0.999). From this we conclude that correlations between potencies of the base species and their octanol:buffer partition coefficients are not unequivocal criteria for identifying the impulse-blocking species of LA.

One problem inherent in the preceding analysis is that it assumes tacitly that there is one site and type of action of LA in impulse blockade, the binding to a sodium channel. Yet LAs also act on potassium channels in nerve (24) and to that degree reduce their impulse-blocking potency (30). A more direct measure of action at a single target site is the inhibition of sodium currents, measured under voltage-clamp, and the assigned LA affinity for the blocking site. The data of Courtney (11) provide the basis for such plots (Figure 7), corrected by the physicochemical values reported here. The concentration of base form of an LA required to halve the sodium current in a resting membrane (i.e., with no preceding use-dependent inhibition) is plotted against P^0 in Figure 7A for two amino-ester and five amino-amide LAs. According to this analysis, the latter class is less potent than the former, by at least 100-fold. When plotted to recognize potential contributions of both protonated and neutral species (Figure 7B), the lines are more nearly

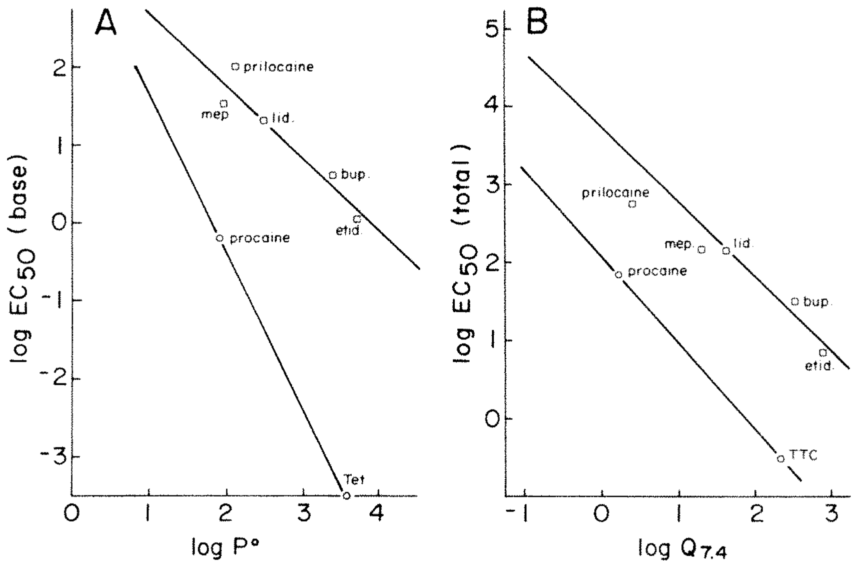

Figure 7. The relationship between LA potency for inhibiting Na^+ currents (in single myelinated axons of amphibian sciatic nerve) and physicochemical properties. **A**, Plots of the log of concentration of LA base (in mM) calculated to halve the current at rest (tonic block, see Reference 14) against log P^0. The line fitting the five amino-amides is (□) $y = 3.66 - 0.938x$ ($r = 0.972$). **B**, When LA potency is expressed as total drug concentration (in mM) and plotted on a log scale against the log of the fraction of total drug distributing into octanol, $Q_{7.4}$, the line for amino-ester (○) compounds becomes more nearly parallel to that for the amino-amides, now fit by $y = 3.75 - 0.954x$ ($r = 0.968$). Potency data from Courtney (Reference 11), measured at 10°C; pK_a, P^0, and $Q_{7.4}$ values from this paper.

parallel and the correlation coefficient for the amino-amides is almost as large as in Figure 7A. These fits also support analyses that include a role for the charged species of LA influenced by extracellular pH, as did the results from impulse blockade. We cannot conclude, therefore, that molecular properties that increase hydrophobicity increase the apparent potency only by making the neutral species of the drug more membrane-permeant.

Finally, we have addressed one mechanism of the reported potentiation of LA action by CO_2:bicarbonate buffer. Although there is a historical controversy concerning the relative clinical efficacies of carbonated versus noncarbonated local anesthetics (31,32), experiments on isolated nerve clearly demonstrate a potentiation by bicarbonate buffer, even at levels of CO_2 (5%) such as occur in expired alveolar air (33,34). One possible mechanism is for bicarbonate to alter the membrane permeability to LA and thereby increase the drug's concentration in the nerve membrane or the cytosol. Our results indicate, however, that to the extent that octanol models the membrane, this particular mechanism is unlikely at 5% CO_2.

Summary and Conclusions

The physicochemical behavior of LAs is a consistent and somewhat predictable function of their structure. Local anesthetic molecules with larger alkyl groups on both the tertiary amine nitrogen and the aromatic moiety show greater hydrophobicity. An ester-linked LA is more hydrophobic and also tends to be more ionized than its amide-linked counterpart, and the addition of a halide to the aromatic ring (as in 2-chloroprocaine) further increases hydrophobicity. When the physicochemical parameters are compared to the primary pharmacologic actions, such as the inhibition of action potentials or ionic currents, a clear correlation between potency and hydrophobicity is observed. This confirms a relationship first reported by Skou in 1954 (10) and elaborated by many since then (see introductory remarks), the consequence of which is that the ability of an LA to penetrate a hydrophobic domain is a determinant of its potency. The hydrophobicity may contribute to potency either by increasing the accessibility of the drug to some functional site in the membrane, i.e., a sodium channel, by increasing the membrane concentration of the drug, or by increasing the actual binding to that site and thus affecting the true affinity.

For clinical applications the physicochemical properties have an additional role, for they determine the ability of LAs to permeate cellular diffusion barriers (e.g., the perineurium) and thus to reach the neural tissue. The degree of ionization and the hydrophobicity determine the uptake and spread of LA and therefore the extent and degree of block. Knowledge of these correlations may allow us to predict and design LAs with tailored rates of onset, duration, and anatomic extent. At the least, octanol:buffer partition coefficients provide a first step in understanding LA:membrane interactions.

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Incendiary Potential of the Flash-Lamp Pumped 585-nm Tunable Dye Laser

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EPSTEIN RH, BRUMMETT RR Jr, LASK GP. Incendiary potential of the flash-lamp pumped 585-nm tunable dye laser. Anesth Analg 1990;71:171–5.

The recently introduced pulsed flash-lamp pumped tunable dye laser is used to treat cutaneous port-wine stains. In our practice, infants and children receive general anesthesia for these brief, yet painful, treatments. Because the flammability of this laser has not been reported and because we administer supplemental oxygen and nitrous oxide, we analyzed the incendiary potential of this laser by measuring the flammability of gauze and Telfa strips, hair, clear plastic face masks and tracheal tubes, and green nasal cannulae in 21%–100% oxygen and in nitrous oxide at laser energies between 6.0 and 10.0 J/cm^2. (Our clinical range is 6.0–7.0 J/cm^2.) In room air, gauze, Telfa, masks, and tubes did not ignite; only gauze ignited at high energy in 100% oxygen. Hair ignited in room air only when struck repeatedly at high energy, but easily ignited in 100% oxygen. Wetting hair with saline prevented ignition in room air and decreased flammability in supplemental oxygen. Green nasal cannulae prongs were extremely flammable in oxygen. Caution should be taken when using supplemental oxygen/nitrous oxide during treatment with the tunable dye laser.

Key Words: SURGERY, LASERS—dye. ANESTHETIC TECHNIQUES, LASERS—dye.

The pulsed flash-lamp pumped tunable dye laser has recently become the preferred treatment of port-wine stains (1), a benign congenital cutaneous vascular ectasia with an estimated frequency of three per 1000 births (2). The laser generates a 585-nm (yellow) pulse that passes through the skin and is absorbed by (red) oxyhemoglobin (which has an absorption peak at 577 nm), causing photothermolysis of the abnormal blood vessels responsible for the port-wine stain (3). (The laser output was changed by the manufacturer within the past year from 577 to 585 nm, which increased the depth of penetration without any decrease in vascular selectivity [4].) Because of the selective nature of absorption, the low absorption of melanin at this wavelength (5), and the brief (450 μs) duration of the pulse, nonspecific heat diffusion and adjacent tissue damage are minimized, and cutaneous scarring is unusual (3). The continuous wave argon laser, formerly used for treatment of port-wine stains, generates blue-green light at 488 and 514 nm, has a minimum exposure time of approximately 200 ms, and causes more widespread tissue destruction and scarring (6). In contrast, the carbon dioxide laser outputs energy at 10,600 nm, a wavelength in the infrared spectrum that is absorbed by water. When used to treat port-wine stains, the carbon dioxide laser causes more extensive tissue damage than either of the other two lasers (7).

Port-wine stains are emotionally often devastating to children because of facial disfigurement and peer reaction (8); and over time, the port-wine stain darkens from faint pink to red-purple, often becoming raised and subject to easy bleeding. Thus, treatment during childhood is optimal. Unfortunately, the laser causes a stinging pain, likened to being snapped with a rubber band, and an accompanying sensation of heat. Adults will usually accept this discomfort; only small areas at a time can be treated in children, however, due to their inability to tolerate the pain. After an unsatisfactory clinical experience by one of the authors (G.P.L.) with a topical anesthetic cream that provided inadequate analgesia and necessitated physical restraint of the children, we were asked to provide anesthesia/analgesia for these procedures. Treatments at 2-mo intervals for approximately 1 yr are required to eliminate a port-wine stain. We have

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elected to administer general anesthesia by mask using oxygen (O_2), nitrous oxide (N_2O), and halothane in infants and children, and intravenous sedation for some older children and adolescents. Each treatment takes 5–20 min, depending on the size of the lesion.

Because the laser is operated in an O_2-enriched environment, we were concerned about the possibility of causing a fire. The incendiary potential of the flash-lamp pulsed tunable dye laser has not been previously reported. The port-wine stain often extends into the hairline and eyebrows, and the eyes need to be protected because of the possibility of retinal damage. We therefore designed this in vitro study to determine the ability of the laser to ignite gauze, hair, and plastic airway equipment in the presence of O_2 and N_2O.

Materials and Methods

A flash-lamp pumped 585-nm pulsed tunable dye laser (Candela Laser Corporation, Wayland, Mass.) with a 5-mm-diameter spot size was used. This laser is designed so that the minimal time between each firing is approximately 2.5 s. Energy output was calibrated with a laser power energy meter (Ophir Optics, Jerusalem, Israel). Single-ply, 1 cm × 1 cm gauze (Johnson and Johnson, New Brunswick, N.J.), 1-cm^2 Telfa pads (The Kendall Company, Boston, Mass.), and dark brown human hair were used as the test materials. Test patches were used dry or saturated with saline or isopropyl alcohol (to simulate the presence of flammable solutions on the skin or hair). Additional targets included a light green nasal oxygen cannula (Marquest Medical Products, Englewood, Colo.), a clear face mask (Vital Signs, Totowa, N.J.), and a 4.0-mm polyvinyl chloride tracheal tube (Malinckrodt, Glenn Falls, N.Y.). The clear plastic and the black markings on the tracheal tube were targeted separately. Oxygen and N_2O were administered from an Ohio 30/70 Proportioner anesthesia machine, and gas concentrations were measured using a Datex 254 Airway Gas Monitor (Datex Medical Instrumentation, Tewksbury, Mass.). Energy output from the laser ranged between 6.0 and 10.0 J/cm^2, the maximum output of the tunable dye laser. Most children are treated clinically with doses between 6.0 and 7.0 J/cm^2. Delivered oxygen concentrations were varied using an Airlife venturi apparatus (American Pharmaseal Company, Valencia, Calif.).

For all test materials except Telfa, the laser energy was adjusted to 6.0 J/cm^2 and then raised in 1-J/cm^2 increments. The output was started at 8.0 J/cm^2 for Telfa. Fresh test samples were used at each energy level. We directed the laser using its 5-mm-diameter aiming light (which is quite accurate) to strike different areas of the target at each energy level, but sites occasionally overlapped. The laser was fired at least three times at each level, or until the test material ignited, whichever came first. After the threshold level at which ignition occurred was determined, 10 additional firings were performed at an energy level 1 J/cm^2 lower using a fresh test sample. If ignition failed to take place, these additional firings were performed at the highest laser output (10 J/cm^2). For the hair samples, the energy level was kept constant and 10 firings were made at 21%, 30%, 40%, 50%, and 100% delivered O_2 concentration, or until ignition occurred; 10 additional firings were then made at the next lowest O_2 concentration. Saline-soaked hair tests were begun at the next O_2 concentration above which hair ignited for each energy level. Fresh hair samples were used at each energy level, O_2 level, wet/dry combination. This procedure was repeated for all laser energy levels tested.

Results

We were unable to ignite gauze or Telfa in room air using the highest tested energy level, even when these materials were soaked in isopropyl alcohol (Table 1). With 100% O_2 directed at the test patch (which resulted in an O_2 concentration of about 85% at the test site), the gauze ignited at 9.0 J/cm^2 but failed to ignite despite 20 pulses at 8.0 J/cm^2; we were unable to ignite the Telfa test patches with 10.0 J/cm^2, even in the presence of 100% O_2. Ignition of gauze at 10 J/cm^2 in the presence of 100% O_2 could be prevented by soaking it with saline. With a 70% N_2O–30% O_2 mixture directed at the gauze test patch, we were unable to cause ignition at 10 J/cm^2. Soaking the gauze or Telfa test patches with isopropyl alcohol allowed ignition at 9.0 and 10.0 J/cm^2, respectively, in the presence of supplemental O_2, but not in room air.

When hair was used as the test material, a small flame and plume of smoke could be seen in room air at energy levels as low as 6.0 J/cm^2, although the hair did not ignite and burn, even at 10.0 J/cm^2, if the laser was carefully aimed not to restrike the same area of hair (Table 2). If the same spot on the hair was repeatedly struck, ignition in room air could be brought about with as little as 8.0 J/cm^2 (unpublished data). As the O_2 concentration of the gas flow directed at the test site was increased from 21% to 100%, ignition of dry hair occurred at lower laser energy outputs. Soaking the hair in saline markedly

Table 1. Ignition of Gauze and Telfa Patches by the Flash-Lamp Pumped 585-nm Tunable Dye Laser

		Samples ignited (*n*)/laser pulses (*n*)					
Laser energy (J/cm^2)	Test material	Room air	Alcohol + room air	100% O_2	Alcohol + 100% O_2	Saline + 100% O_2	70% N_2O + 100% O_2
6.0	Gauze	0/3	0/3	0/3	0/3	0/3	0/3
7.0	Gauze	0/3	0/3	0/3	0/3	0/3	0/3
8.0	Gauze	0/3	0/3	0/20	0/10	0/3	0/3
9.0	Gauze	0/3	0/3	1/5	1/9	0/3	0/3
10.0	Gauze	0/10	0/10	2/5	1/7	0/10	0/10
8.0	Telfa	0/3	0/3	0/3	0/3	0/3	0/3
9.0	Telfa	0/3	0/3	0/3	0/10	0/3	0/3
10.0	Telfa	0/10	0/10	0/10	1/3	0/10	0/10

Alcohol = isopropyl alcohol.
Column headings indicate solution test material was soaked in (if any), and gas directed at test site.

Table 2. Ignition of Dry or Wet Hair by the Flash-Lamp Pumped 585-nm Tunable Dye Laser in Various Oxygen Concentrations

Laser energy (J/cm^2)	% Oxygen	Samples ignited (*n*)/laser pulses (*n*)	
		Dry hair	Wet hair
6.0	21–30–40[a]	0/30	ND
6.0	50	0/20	ND
6.0	100	1/2	0/20
7.0	21–30–40[a]	0/30	ND
7.0	50	0/20	ND
7.0	100	1/1	0/20
8.0	21–30[a]	0/20	ND
8.0	40	0/20	ND
8.0	50	1/7	0/20
9.0	21	0/20	ND
9.0	30	1/9	ND
9.0	40	1/3	ND
9.0	50	ND	0/20
9.0	100	ND	1/10
10.0	21	0/20	ND
10.0	30	1/6	ND
10.0	40	ND	0/20
10.0	50	ND	1/7

ND, not determined.
[a] Laser was fired 10 times at each oxygen concentration listed.

Table 3. Ignition of Plastic Airway Materials by the Flash-Lamp Pumped 585-nm Tunable Dye Laser

Laser energy (J/cm^2)	Test material	Test materials ignited (*n*)/laser pulses (*n*)	
		O_2 via lumen	O_2 external
6.0–9.0[a]	Face mask	0/12	0/12
10.0	Face mask	0/10	0/10
6.0–9.0[a]	ETT	0/12	0/12
10.0	ETT	0/10	0/10
6.0	NC	0/3	2/2
7.0–9.0[a]	NC	0/9	ND
10.0	NC	0/10	ND

ETT, endotracheal tube; NC, nasal cannula; ND, not determined.
[a] Three laser pulses were fired at each energy within the range given.

diminished the flammability of the hair in supplemental O_2, but ignition could be brought about at energy levels of 9.0 J/cm^2 or more. Although nonoverlapping areas of hair were targeted, the sample became friable and dried out somewhat during the multiple laser firings, which may have contributed to its ignition.

The clear face mask and tracheal tube did not ignite at 10 J/cm^2 with 100% O_2 either flowing through the lumen or directed externally at the test site (Table 3). When the black markings on the tracheal tube were hit, the markings vaporized with an audible snap, but no flame and no ignition of the adjacent plastic occurred. When 100% O_2 was directed through the lumen of the nasal cannula and the tip of the cannula was targeted, ignition did not occur. However, when O_2 was directed externally at this test site, ignition occurred at 6 J/cm^2.

Discussion

Despite the brief duration (<0.5 ms) of the tunable dye laser output, sufficient energy is absorbed at the lowest clinically used setting (6 J/cm^2) to ignite dry hair if 100% O_2 is directed at the target site. This can be prevented when the hair is soaked with saline. Because port-wine stains often extend into the eyebrows or the scalp, it is not uncommon for hair to be struck by the laser. In the several hundred patients we have treated, hair has never ignited, but it is frequently singed. Clear plastic will not ignite, not even in 100% O_2, but green plastic easily ignited when O_2 was directed at the target site. These differences are due to the fact that the tunable dye laser outputs light in the visible spectrum (yellow), which is transmitted rather than absorbed by clear materials. Darker materials absorb enough energy to produce sufficient heat for combustion.

The flammability of hair has important implications for dermatologists using the tunable dye laser where anesthesia or analgesia is administered in the presence of supplemental O_2 or N_2O. Even when supplemental O_2 is not being administered, it would be prudent to wet hair adjacent to the port-wine stain with saline or water. We have also used white petroleum jelly for this purpose, but it does not appear to work any better than water in reducing the flammability of hair in supplemental O_2 (unpublished data). In the course of these experiments, we accidentally set a plastic circuit on fire when a gauze strip ignited; one can imagine the potential patient injury that would occur if a nasal cannula or plastic mask ignited while a patient was being treated.

Because of the potential for causing a fire, one should not direct supplemental O_2 or N_2O into the laser field. Because the port-wine stain is usually on the face, this requires a tight mask fit; the mask should be removed from the face when lesions around the mouth, nose, and eyes need to be treated. Leakage of O_2 under the mask can be minimized by maintaining spontaneous respiration and avoiding positive pressure ventilation; we find use of a mask with a soft, air-filled cushion particularly useful in attaining a good seal. We have tested O_2 leaking under the mask under these conditions and found concentrations of 21%–28% at the bridge of the nose, and 21%–22% over the forehead, during administration of 100% O_2 and halothane (unpublished data). Tracheal intubation might be considered in these patients to further minimize the risk of setting hair on fire, but it should be emphasized that these measured concentrations of O_2 are far less than required (at least >50%) in the clinical laser dose range (6.0–7.0 J/cm^2) to support ignition. Because of the extremely brief nature of most treatment sessions, the low laser energy levels utilized clinically, and the need for high O_2 concentrations to support ignition at these energy levels, we believe that the risks involved in administering anesthesia by mask relative to the risks of tracheal intubation are reasonable. If one is going to do these cases by mask, it would be a good idea to check the O_2 concentration around the mask using a portable O_2 analyzer, and adjust one's technique accordingly in the presence of large leaks. It is preferable, however, to use an O_2/air mix rather than O_2/N_2O to minimize the delivered concentration of combustion-supporting gases.

When facial lesions are being treated, use of green nasal cannulae is ill-advised. Lack of flammability in vitro of different colored cannulae should be verified before use. Saline-soaked Telfa pads rather than gauze should be used to protect the eyes, and care should be taken not to hit the pads with the laser beam. Extreme care must be taken not to direct O_2 or N_2O into the laser field when this is adjacent to eyebrows or the scalp. Although soaking the hair in saline minimizes the risk of ignition in room air, wetness of the hair needs to be maintained and care should be taken not to repeatedly strike the same area of hair. Although saline-soaked hair could be ignited in 100% O_2 at a laser energy of 9.0 J/cm^2 or above, this is far in excess of the level used to treat pediatric patients.

Because the clear plastic airway materials we tested would not ignite even in the presence of 100% O_2, such items would appear to be relatively safe. The amount of light energy absorbed by colored plastic (and hence heat-produced) will vary according to the particular color involved and the intensity of the color, so laser output thresholds for ignition are likely to be relatively device-specific. We recommend substituting clear for colored plastic airway products wherever possible during operation of the tunable dye laser.

Because isopropyl alcohol enhances the flammability of both gauze and Telfa, cleaning the skin with inflammatory substances before the laser treatment should be avoided, as should the use of any potentially flammable substance on the skin or hair near the treatment area.

In conclusion, we have demonstrated a potential hazard of the tunable dye laser when operated in an O_2-enriched environment. Hair, gauze, and colored plastic airway products are at risk for igniting when O_2 is directly applied to the target site; clear airway products will not ignite, even at laser energies far in excess of clinical use. Care should be taken not to allow O_2 or N_2O to flow over the treatment site when the tunable dye laser is in operation.

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High Spinal Anesthesia Does Not Depress Central Nervous System Function as Measured by Central Conduction Time and Somatosensory Evoked Potentials

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LANG E, ERDMANN K, GERBERSHAGEN HU. High spinal anesthesia does not depress central nervous system function as measured by central conduction time and somatosensory evoked potentials. Anesth Analg 1990;71:176–80.

Short-latency somatosensory evoked potentials (SSEPs) in response to median nerve stimulation were recorded from the neck and the scalp before and during diagnostic high spinal anesthesia (touch T3, pinprick C8) in six patients with chronic pain. The central conduction time—the time difference between the neck-recorded N13 and the scalp-recorded N20—and the amplitudes of the SSEPs did not change in a statistically significant way during high spinal anesthesia. However, latencies of the neck-recorded N13 and the scalp-recorded N20 and P25 increased slightly. This may have been due to a local anesthetic effect on those spinal roots of the median nerve in which segmental pinprick analgesia occurred. Because high spinal anesthesia did not depress central nervous function, as measured by central conduction time, and SSEP amplitudes, it is concluded that scalp-recorded SSEPs during high spinal anesthesia measure the effects of local anesthetics in the cerebrospinal fluid on neuronal pathways outside the brain.

Key Words: ANESTHETIC TECHNIQUES, SPINAL—CNS function. BRAIN, EVOKED POTENTIALS.

Short-latency somatosensory evoked potentials (SSEPs) recorded from the scalp have been used in spinal and epidural anesthesia to measure local anesthetic effects at the spinal level (1–5). There are no data on the influence of cerebral effects of spinal anesthesia on SSEPs. However, such effects are suggested as patients, particularly with anesthesia at high sensory levels, frequently become sleepy during spinal anesthesia (6–8). Also, the level of consciousness may influence the SSEPs (9–11). Although sleep patterns have not been recorded during high spinal anesthesia (HSA) with the electroencephalogram (8), effects of spinal anesthesia on the brainstem (7) may subclinically exist.

To evaluate possible cerebral effects of diagnostic HSA on SSEPs, we measured neck- and scalp-recorded SSEPs after median nerve stimulation before and during HSA to T3. We also determined the central conduction time (CCT), which provides information on the integrity of the central neuronal pathways between the lower brainstem and the cortex (12,13).

Materials and Methods

Patients

Studies were performed on six patients with their informed consent. All patients suffered from chronic pain in the lower half of the body. High spinal anesthesia was performed to assure the physician and to demonstrate to the patient that the origin of the pain lay outside the peripheral nervous system.

Stimulation and Recording

Both median nerves were stimulated alternately at the wrist via bipolar surface electrodes (5.1 stimuli/s, stimulus duration 0.2 ms, current intensity at 4 mA above motor threshold).

Median nerve evoked SSEPs were recorded simultaneously from subcutaneous needle electrodes inserted at the spinous processus C7, at the scalp in positions C3′ and C4′, and at Fpz as reference (10–20 system). The signals were then filtered (bandpass,

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Table 1. Patient Data, Anesthesia Level (Touch and Pinprick Sensation), and the Effect of High Spinal Anesthesia on Pain and Tiredness

Case	Sex	Age (yr)	Height (cm)	Pain area	Anesthesia level		Pain	Tiredness
					Touch	Pinprick		
1	M	66	176	Right foot	T4	T1	Abolished	Marked
2	M	32	176	Low back Left leg	T2	C6	Persisted	None
3	F	26	177	Low back Hips, knees	T2	C8	Persisted	Marked
4	F	29	170	Left leg	T2	C7	Persisted	Marked
5	M	33	178	Low back Coccyx	T5	T1	Persisted	None
6	F	62	163	Right leg	T3	T1	Abolished	None

HSA, high spinal anesthesia.

5–3000 Hz), averaged (250 stimulus responses), and recorded for 80 ms after stimulus onset. Somatosensory evoked potentials evoked by stimulation of both median nerves were recorded a minimum of six times before and two to four times within any 10-min interval during HSA (0–70 min). The signals were stored on disk for off-line analysis. All neurophysiologic measurements were performed with the electrodiagnostic system, Pathfinder I (Nicolet).

High Spinal Anesthesia

The patients were unpremedicated. The cardiovascular system was monitored continuously by electrocardiogram and oscillometric blood pressure measurements (Dinamap, Critikon). After infusion of 1500 mL of electrolyte solution and intravenous injection of 0.5 mg of atropine sulfate, HSA was induced. In the right lateral recumbent and 5° Trendelenburg position, 2 mL of hyperbaric 5% articain (Ultracain, Hoechst) was injected through a 25-gauge spinal needle into the subarachnoid space at L4. Patients were then turned to the supine position, and the level of anesthesia (loss of cold, pinprick, and touch sensation) was adjusted by changing the degree of the head-down tilt of the operating table. Patients were then asked repeatedly about the sensation of pain and feeling of tiredness. The feeling of tiredness was graded as none, little, or marked.

Data Analysis

We measured the peak latencies (N20, P25, N35, P45) and the interpeak amplitudes (N20/P25, P25/N35, N35/P45) of the scalp-recorded SSEPs. We also measured the latency and the baseline-to-peak amplitude (12) of the major negative peak of the neck potential (13,14), which we refer to as N13 (14,15). Finally, we determined the CCT as the time difference between the cervical N13 and the cortical N20. The averages of the parameters were measured before HSA and within any 10-min interval during HSA.

Statistical Analysis

A nonparametric analysis of variance (Friedman ANOVA by ranks) was used to identify a statistically significant difference in latency or amplitude at any time interval. Where statistically significant differences were detected, multiple comparisons (Wilcoxon-Wilcox test) were performed. $P < 0.05$ was considered statistically significant.

Results

Patient data, anesthesia levels, and the effect of HSA on pain and tiredness are summarized in Table 1. On average, the upper level of the loss of pinprick sensation (mean C8) exceeded that of the loss of touch sensation (mean T3) (Table 1) by three segments. There was no correlation between the effects of HSA on pain and tiredness ($r = 0$, coefficient phi, $n = 6$). The maximal decrease in mean arterial blood pressure (Figure 1) was 23% after the induction of HSA.

The latencies and amplitudes of SSEPs before and during HSA are given as their means of the numerical values (Table 2) and are also given as their means of the intraindividual differences compared with the respective values before HSA (Figure 1). The mean latencies of the neck-recorded N13 and the scalp-recorded N20 and P25 increased slightly, but almost

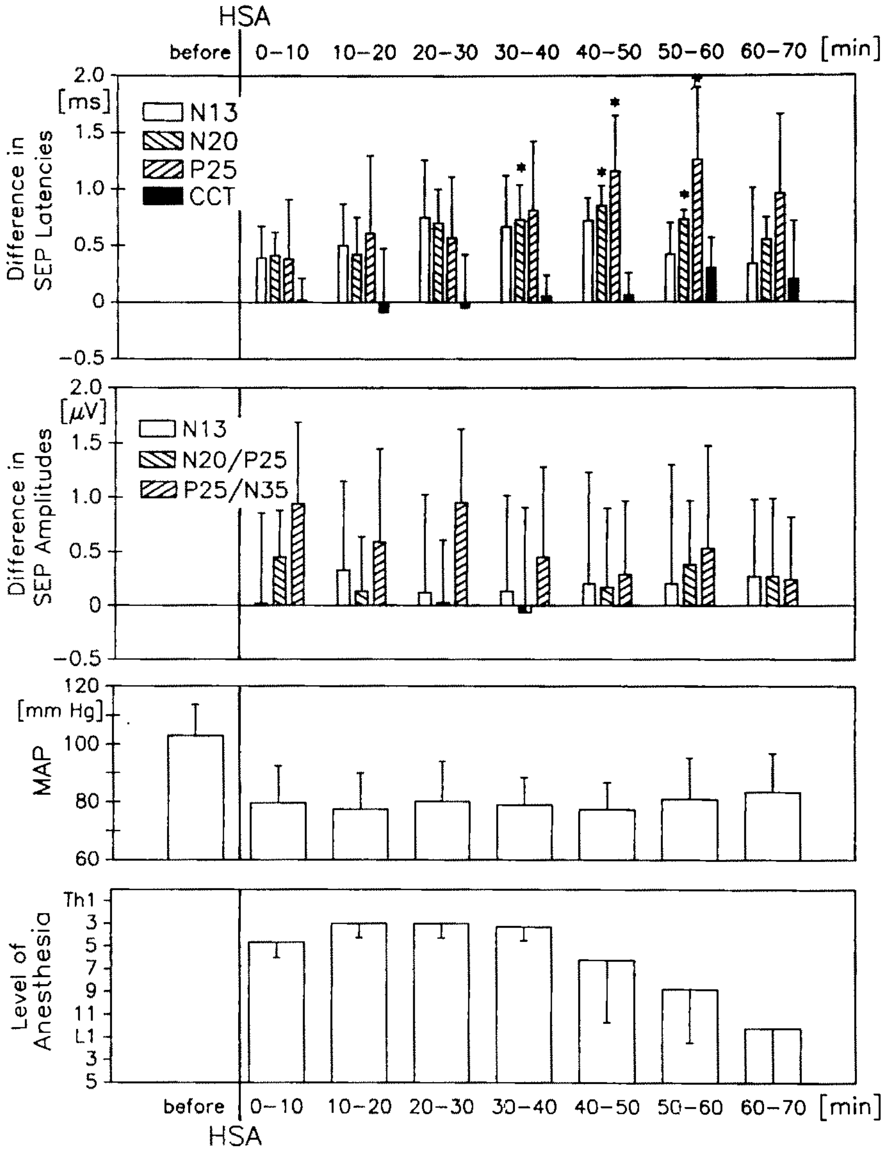

Figure 1. Latencies and interpeak amplitudes of SSEPs, mean arterial blood pressure (MAP, mm Hg), and anesthesia level (touch) before and during high spinal anesthesia (HSA) (mean ± SD, $n = 6$). The amplitudes and latencies are plotted as differences between the values of each time interval and the respective value before HSA. *Different from values before HSA in a statistically significant way ($P < 0.05$).

parallel to each other, after induction of HSA up to the 50–60-min time interval (Table 2, Figure 1). N20 and P25 latencies differed significantly from the values before HSA between the 30–60-min and 40–60-min time intervals, respectively.

In contrast, CCT did not show such changes in latency. There was only a minimal change compared with the values before HSA (Table 2, Figure 1). The changes in the latencies of N13 and scalp-recorded N35 and P45 were not statistically significant.

The amplitudes of neck- and scalp-recorded SSEPs showed considerable inter- and intraindividual variations (Table 2, Figure 1). The mean amplitudes of N13, N20/P25, and P25/N35 were generally increased throughout HSA (Figure 1), but at no time intervals were the differences statistically significant from the values before HSA. The mean amplitudes of N35/P45 did not show consistent changes (Table 2).

Discussion

Our SSEP values before HSA correspond well with other normative data (12,13,15), and our differences in the level between loss of touch and pinprick sensation agree with previous findings (16).

Neither CCT, a recognized measure of conduction in central pathways in the brain (13), nor the amplitudes of the cortical evoked potentials after median nerve stimulation were significantly affected by HSA. Apart from clinical and pharmacologic grounds (7), our data provide a further argument against any

Table 2. Latencies (ms) and Interpeak Amplitudes (μV) of Neck- and Scalp-Recorded Somatosensory Evoked Potentials (mean ± SD, n = 6) Evoked by Alternated Stimulation of Both Median Nerves Before and During High Spinal Anesthesia

SSEP parameters	Before HSA	During HSA 0–10 min	10–20 min	20–30 min	30–40 min	40–50 min	50–60 min	60–70 min
Neck-recorded								
N13 (ms)	14.90 (±0.69)	15.30 (±0.69)	15.41 (±0.50)	15.66 (±0.69)	15.57 (±0.71)	15.63 (±0.75)	15.33 (±0.74)	15.25 (±0.70)
N13 (μV)	1.55 (±1.08)	1.57 (±0.72)	1.88 (±0.78)	1.67 (±0.38)	1.68 (±0.69)	1.75 (±1.10)	1.75 (±0.74)	1.82 (±0.55)
Scalp-recorded								
N20 (ms)	20.55 (±0.55)	20.96 (±0.70)	20.97 (±0.62)	21.25 (±0.80)	21.28 (±0.67)[a]	21.40 (±0.64)[a]	21.28 (±0.60)[a]	21.10 (±0.48)
P25 (ms)	25.91 (±2.16)	26.29 (±2.10)	26.52 (±1.94)	26.48 (±2.01)	26.72 (±1.83)	27.08 (±2.00)[a]	27.17 (±1.90)[a]	26.87 (±1.85)
N35 (ms)	35.12 (±2.17)	37.09 (±3.44)	36.61 (±1.87)	36.52 (±2.19)	36.94 (±2.37)	36.06 (±2.54)	36.55 (±2.07)	36.10 (±1.71)
P45 (ms)	43.34 (±4.22)	46.07 (±3.66)	45.58 (±3.11)	46.26 (±3.28)	47.24 (±3.68)	46.20 (±3.87)	46.95 (±4.24)	45.59 (±3.16)
N20/P25 (μV)	2.99 (±1.04)	3.44 (±1.27)	3.12 (±0.87)	3.03 (±0.67)	2.93 (±1.23)	3.16 (±1.52)	3.38 (±1.43)	3.26 (±1.07)
P25/N35 (μV)	2.85 (±0.92)	3.79 (±1.35)	3.45 (±1.39)	3.80 (±1.27)	3.30 (±0.85)	3.14 (±0.66)	3.39 (±1.39)	3.09 (±0.93)
N35/P45 (μV)	2.45 (±1.58)	2.23 (±1.35)	2.28 (±1.01)	2.60 (±0.83)	2.75 (±1.01)	2.20 (±1.10)	2.41 (±1.36)	2.35 (±1.07)
CCT (ms)	5.65 (±0.41)	5.66 (±0.26)	5.56 (±0.41)	5.59 (±0.25)	5.70 (±0.33)	5.71 (±0.39)	5.94 (±0.59)	5.85 (±0.67)

SSEPs, short-latency somatosensory evoked potentials; HSA, high spinal anesthesia; CCT, central conduction time.
[a] Different in a statistically significant way compared with values before high spinal anesthesia ($P < 0.05$).

relevant diffusion of local anesthetic into the brainstem or cortex. Furthermore, the degree of hypotension in our patients, as in the findings of others during HSA (17), did not result in hypoxic depression of the brain. This agrees with the measurements of electroencephalogram amplitudes in humans, which decreased in a pressure-dependent manner only when mean arterial blood pressure decreased below 57 mm Hg (18).

Because CCT remained unchanged, the mechanisms for the slight latency shift of the cortical N20 and P25 need to be localized distally to the generator of N13. A slowing down of N13 latency may be developed by a partial conduction block of the spinal roots of the median nerve (C5-D1) (19) in dermatomes in which loss of pinprick sensation occurred. This explanation is in accordance with SSEP latencies measured during spinal or epidural anesthesia without the loss of touch sensation (1–4). In contrast to the SSEP amplitudes measured after stimulation in the spinal segments that are most intensely blocked by spinal or epidural anesthesia (1–4), the mean amplitude of the N13 potential did not decrease in our patients. This suggests that the myelinated fibers of the median nerve roots were not measurably blocked by the local anesthetic. In addition, the slow time-course of the slight increase in the latencies of the cortical N20 and P25, which did not reach statistical significance until 30 min after the induction of HSA, suggests a low concentration of the local anesthetic in the lower cervical segments.

Although we did not measure temperature, the SSEP changes are unlikely to be affected by a temperature change. There was an increase in both the latencies and the amplitudes, except for CCT and N35/P45, and the changes tended toward control at the end of HSA. As has been reported before, mild (20), moderate (21), and marked (22) hypothermia result in progressive prolongation of latencies and a decrease in amplitudes. Thus, if the patients had cooled during HSA the increase in amplitude would be in conflict with these findings (20–22).

The SSEPs during HSA also differ from the changes during physiologic sleep. A progressive increase in latencies (9–11) and a decrease in amplitudes (10) of the primary cortical complex of the SSEPs after median nerve stimulation has been observed to occur from the waking to stage 4 sleep. This corresponds to the absence of sleep patterns in the electroencephalogram during HSA (8).

In conclusion, we observed no effect of HSA on central nervous function as measured by CCT and cortical SSEP amplitudes. Thus, the scalp-recorded SSEPs during HSA indicate the effects of local anesthetics used to produce spinal anesthesia on neuronal pathways outside the brain, if profound hypotension does not occur.

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Effects of Halothane on Intraocular Pressure in Anesthetized Children

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WATCHA MF, CHU FC, STEVENS JL, FORESTNER JE. Effects of halothane on intraocular pressure in anesthetized children. Anesth Analg 1990;71:181–4.

Intraocular pressure (IOP) measurements in children are usually performed under nitrous oxide and halothane anesthesia. We studied the effects of both time and end-tidal halothane concentration on IOP in 80 children (mean age ± SD = 4.5 ± 2.9 yr), to determine the most optimal time to make such measurements in anesthetized children. In 30 children the end-tidal halothane and nitrous oxide concentrations were kept constant while IOP was measured at 1-min intervals after the induction of anesthesia. Intraocular pressure did not change with time. In another 50 children IOP was measured immediately after induction, after 10 min of steady-state end-tidal halothane concentrations of both 0.5% and 1.0% in 66% nitrous oxide, and immediately after tracheal intubation. Intraocular pressure did not differ significantly at either halothane concentration but increased after tracheal intubation. We conclude that in patients anesthetized with halothane and nitrous oxide, IOP after induction remains constant over time and is not affected by end-tidal halothane concentrations up to 1.0% but is affected by tracheal intubation. Thus, the optimal time to measure IOP in children receiving up to 1% halothane in 66% nitrous oxide is during the first 10 min after induction, but before tracheal intubation.

Key Words: ANESTHESIA, PEDIATRIC—intraocular pressure. EYE, INTRAOCULAR PRESSURE. ANESTHETICS, VOLATILE—halothane.

Accurate serial intraocular pressure (IOP) measurements are essential for the diagnosis and treatment of glaucoma. In awake, struggling, uncooperative infants and children, reliable measurements of IOP are difficult to obtain. Hence, these patients are often examined under heavy sedation or general anesthesia. The anesthetic technique used must not affect IOP because therapeutic decisions are based on this measurement. In adults IOP is reduced below preinduction levels by a variety of induction agents (1). However, the time-course of anesthetic-induced changes in IOP has not been previously studied.

In children, probably the most common anesthetic agents used are nitrous oxide (N_2O) and halothane. Although halothane can cause a dose-dependent reduction in IOP in adults (1–4), studies in children have provided conflicting data (5–7). We designed this study to determine the effects of duration of anesthesia and halothane concentration on the IOP in children anesthetized with halothane and N_2O. Such data should help in determining the optimal timing of IOP measurements after the induction of anesthesia.

Materials and Methods

After obtaining institutional approval and written informed consent from parent or legal guardian of the child, we studied 80 children, ASA physical status I or II, scheduled for elective eye-muscle surgery. We excluded patients with a history of central nervous or other major system disease, children in whom the use of halothane was contraindicated, and children under 6 mo of age or 5 kg of body weight.

No preanesthetic sedative medications were administered. After fasting for a minimum of 6–8 h, all patients were anesthetized with halothane in 66% N_2O. A Bain modification of a Mapleson D circuit was

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used in children below 20 kg, and a circle absorber system in larger children. Heart rate, arterial blood pressure, temperature, and oxygen saturation were measured by standard methods. Inspired and expired gas samples were obtained from a catheter placed in the oropharynx (8). The concentrations of nitrogen, oxygen, N_2O, carbon dioxide (CO_2), and halothane in these samples were analyzed by a mass spectrometer (Perkin-Elmer MGA 1100 mass spectrometer, Perkin-Elmer, Pomona, Calif.) that had been calibrated with gases analyzed to an accuracy of ±0.02% (Scott Medical Products, Plumsteadville, Pa.). If the end-tidal nitrogen concentration exceeded 0.5%, the oropharyngeal catheter and the seal around the face mask were adjusted to exclude contamination by ambient air. Under these circumstances, the oropharyngeal gas samples have been shown to be representative of samples drawn from the distal end of the endotracheal tube in children over 6 mo of age and 5 kg body weight (8).

After induction of anesthesia, the end-tidal CO_2 tension was maintained between 32 and 45 mm Hg using positive pressure ventilation (peak inspiratory pressure less than 20 cm H_2O and zero end-expiratory pressure). Each patient was in the supine and horizontal position throughout the study. At all times pressure on the eyes by the face mask was avoided.

All IOP measurements were made by one of two investigators (F.C.C. or J.L.S.) using a Perkin's hand-held applanation tonometer after fluorescein was instilled in the conjunctival sac. Because of the young age of the patients a baseline IOP measurement in each eye was performed immediately after the induction of general anesthesia and the return of the eyes to a primary midline position.

The study was performed in two phases. In phase 1, 30 patients were studied to determine the relationship between time and IOP after the induction of anesthesia. In this phase we maintained stable end-tidal N_2O and halothane concentrations, while IOP was measured at 1-min intervals for 10 min. The mean (±SD) end-tidal N_2O and halothane concentrations during these measurements were 66.5% ± 3.9% and 1.31% ± 0.33%, respectively. Although there were interpatient differences in the end-tidal halothane concentration during this phase, the concentration in each patient was held constant (±0.05%) during the 10 min of IOP measurement.

In phase 2, we studied 50 patients to determine the effects of increasing the halothane concentration on IOP. Intraocular pressure of all patients in the second phase was measured in triplicate at baseline as described above, and after 10-min periods of a constant end-tidal halothane concentration of 0.5% ± 0.05% and 1.0% ± 0.05%, respectively. Patients were randomized so that 25 subjects had IOP measured first at an end-tidal halothane concentration of 0.5% and then at 1.0%; the other 25 subjects had IOP measured first at 1.0% and then at 0.5% halothane. Atracurium (0.5 mg/kg) was then administered intravenously and the trachea intubated when there was no response of the adductor pollicis to a 5-s 50-Hz supramaximal tetanic stimulus. The IOP was remeasured within 30 s of tracheal intubation.

For the purposes of statistical analysis we did not pool data from both eyes, as IOP in one eye was not totally independent of IOP in the other eye of the same patient. The data were divided into sets relating to the left eye and to the right eye, respectively, and separate analyses were performed on each data set. Intraocular pressure values at 1-min intervals in phase 1 subjects were compared by a one-factor repeated-measures analysis of variance. In phase 2 subjects the mean IOP values at baseline, 0.5% and 1% halothane, and after tracheal intubation were compared by paired Student's *t*-tests with Bonferroni corrections for multiple tests, and by a one-factor repeated-measures analysis of variance. If the hypothesis of equal population means was rejected, a Scheffe's test was performed for multiple comparisons of individual group means. Statistical significance was accepted at a *P* value of ≤0.05.

Results

The mean age (±SD) of the subjects studied was 4.5 ± 2.9 yr. The mean time between loss of eyelash reflex and the return of the eyes to the midline position was 1.47 ± 0.71 min. As mentioned above, we used separate data sets for each eye to avoid counting the same patient twice. Figure 1 and Table 1 provide data from the left eye. This was an arbitrary choice, but the conclusions were not altered by using either data set. This should not be surprising as there were no statistically significant differences between IOP values in the two eyes of the same patient.

In phase 1 patients there were no significant changes in baseline IOP when measured on a minute-by-minute basis over 10 min, while the end-tidal halothane and N_2O concentrations were kept constant and the child was not stimulated (Figure 1). The initial mean IOP was 7.9 ± 3.7 mm Hg, and the final mean IOP (at 10 min) was 8.0 ± 2.8 mm Hg ($P = 0.7$). There was no significant correlation between the IOP and the end-tidal halothane concentration at which the study was performed. This lack of correlation

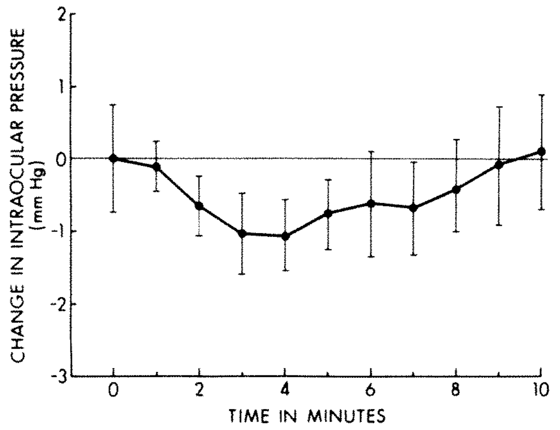

Figure 1. The relationship between time after induction of anesthesia and changes in IOP from baseline levels during steady-state end-tidal halothane and N_2O concentrations (mean ± SEM). Time 0 measurements were performed immediately after induction of anesthesia and the return of the eyes to a neutral midline position (see text).

occurred when the end-tidal halothane concentration was expressed as a percentage of alveolar gas or as a multiple of the age-appropriate MAC (8,9).

The 50 patients studied in phase 2 were divided into three age groups for which data on MAC are available (9): (a) between 6 mo and 2.5 yr, (b) 2.6–7 yr, and (c) 7.1–12 yr. There were no significant differences between IOP measured at an end-tidal halothane concentration of 0.5% and that measured at 1.0% in the presence of 66% N_2O in any of the three age groups or in pooled data. In these three age groups, an end-tidal halothane concentration of 0.5% represents 0.52, 0.55, and 0.56 MAC, respectively, whereas 1.0% halothane represents 1.03, 1.10, and 1.15 MAC, respectively. Therefore, in the presence of 66% N_2O, IOP was not significantly altered by increasing halothane from 0.52 MAC to 1.03 MAC in children between 6 mo and 2.5 yr, from 0.55 MAC to 1.10 MAC in children between 2.6 and 7 yr, and from 0.56 MAC to 1.15 MAC in children between 7.1 and 12 yr. However, after tracheal intubation there was a significant increase in IOP in each age group and in pooled data (Table 1).

Discussion

Intraocular pressure measured after the induction of anesthesia has been reported to be lower than preinduction values in adults and in some studies in children (1–4). Apparent changes, especially decreases in IOP from preinduction values in anesthetized children, may represent elevated baseline values obtained in struggling, uncooperative patients rather than a response to halothane (5). Even cooperative patients tend to tense the extraocular muscles and consequently increase the baseline levels when a tonometer is brought close to the eyes to measure IOP. This may explain the reported decrease in IOP after induction of anesthesia (1). Studies in well-sedated children (5) and in children anesthetized with thiopental or cyclopropane (6) have shown that the addition of halothane did not cause a significant change in the IOP from baseline values (5,6).

The present study indicates that postinduction IOP during halothane-N_2O anesthesia remains constant for at least 10 min after the eyes have returned to a neutral position. If IOP decreased during anesthesia in our subjects, these changes must have occurred rapidly, in the short time between induction and the return of the eyes to the midline position, as subsequent IOP values were constant. Because IOP did not change with time during steady-state anesthesia, IOP in anesthetized, unstimulated children may be measured any time in the first 10 min after induction.

As a result of the poor correlation between IOP and the end-tidal halothane concentration in our initial (phase 1) study, we evaluated the halothane-IOP dose-response. We maintained steady-state end-tidal halothane concentrations of 0.5% and 1% for at least 10 min before the IOP measurement to permit

Table 1. Intraocular Pressures in the Left Eye After Induction of Anesthesia (Baseline), After Exposure to 0.5% and 1% Halothane, and After Tracheal Intubation in Each Age Group

Age range (yr)	Patients (*n*)	IOP (mm Hg)[a] Baseline	0.5% Halothane	1% Halothane	After intubation
0.5–2.5	15	7.9 ± 4.1	8.6 ± 3.7	8.4 ± 3.5	16.0 ± 3.9[b]
2.6–7.0	26	9.4 ± 2.6	11.0 ± 2.2	10.6 ± 2.0	18.8 ± 4.9[b]
7.1–12	9	11.9 ± 5.2	11.7 ± 3.1	11.1 ± 3.6	16.8 ± 8.4[b]
Total	50	9.3 ± 3.8	10.3 ± 3.1	10.0 ± 3.0	17.6 ± 5.2[b]

IOP, intraocular pressure.

[a] All values are mean ± SD.

[b] $P < 0.05$ for postintubation IOP versus baseline IOP and IOP at 0.5% and at 1.0% end-tidal halothane in 66% nitrous oxide.

equilibration of the brain anesthetic concentrations (10). In contrast to previous studies in adults (2–4,11,12) and to one study in children (13), we failed to demonstrate a dose-dependent effect of halothane on IOP. In the pediatric study by Hetherington and Shaffer, mean IOP levels in children with or without glaucoma decreased as the depth of halothane anesthesia increased (13). Because details of their anesthetic technique and statistical analysis were not provided, it is possible that these authors studied patients at a deeper level of anesthesia than we did. A dose-related effect may or may not be present at end-tidal halothane concentrations less than 0.5% or greater than 1.0%. However, baseline levels in our patients were low and resembled episcleral venous pressures. This may indicate that there is a marked hyposecretion of the aqueous humor during halothane-N_2O anesthesia and that a further increase in the halothane concentration may not result in a greater reduction in IOP (12,13).

It is also possible that IOP responses to halothane anesthesia differ in children and in adults. However, there are no data on age-related dose-response curves of halothane and IOP. Age-related differences in the dose-response interactions have been reported in studies on movement with skin incision (MAC) (9), and on airway responses to tracheal intubation (8) in subjects anesthetized with halothane. Although data from studies on one response should not be extrapolated to another response, it is possible that the halothane-IOP dose-response also varies with age. To rule out the possibility that our dose-response results were obscured by having a large age range in our subjects, we reanalyzed our data after dividing the patients in phase 2 into three age groups, similar to those used in MAC and in tracheal intubation studies (8,9). One-factor repeated-measures analysis of variance performed separately for each age group yielded the same results as for our pooled data. Thus, it would appear that the age distribution of the subjects did not affect conclusions. Finally, because the stimulus of tracheal intubation was associated with a significant increase in IOP as has been reported previously (5–7, 11–15), we recommend that IOP in anesthetized children be measured before tracheal intubation.

In summary, we conclude that in normal children anesthetized with halothane and N_2O, IOP remains stable during the first 10 min after the return of the eyes to a neutral midline position. Intraocular pressure is not affected by a rise in the end-tidal halothane concentration from 0.5% to 1.0%, but is increased after tracheal intubation. Under commonly used doses of N_2O and halothane, IOP measurements may be obtained at virtually any convenient time before tracheal intubation.

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Vecuronium for Rapid-Sequence Intubation for Cesarean Section

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HAWKINS JL, JOHNSON TD, KUBICEK MA, SKJONSBY BS, MORROW DH, JOYCE TH III. Vecuronium for rapid-sequence intubation for cesarean section. Anesth Analg 1990;71:185–90.

Because succinylcholine may occasionally be contraindicated for rapid-sequence induction in parturients, we studied the use of vecuronium in 21 patients having elective cesarean sections. Eleven patients (group 1) received 10 μg/kg vecuronium as a priming dose, followed 4–6 min later by 100 μg/kg. Ten patients (group 2) received 200 μg/kg vecuronium as a bolus. Onset, the time from the injection of vecuronium to maximal twitch suppression, and clinical duration, the time between vecuronium administration and return to 25% of the control twitch height, were recorded. Umbilical and maternal venous blood samples at delivery were analyzed for vecuronium concentrations. One-minute and 5-min Apgar scores and 1- and 24-h Neurologic and Adaptive Capacity Scores (NACS) were recorded. Individual tests of passive and active tone within the overall NACS profile were compared to evaluate further any residual vecuronium effects in the infants. Onset of neuromuscular blockade was 177 s in group 1 and 175 s in group 2. The corresponding clinical durations were 73 and 115 min. Maternal and umbilical venous vecuronium concentrations were 515 and 73 ng/mL in group 1 and 838 and 107 ng/mL in group 2. Seventy percent of neonates in group 1 had Apgar scores greater than 7 at 1 min, with 100% greater than 7 at 5 min. Corresponding values in group 2 infants were 50% and 80%. Fifty percent of group 1 infants had NACS of 35–40 at 1 h, and 70% at 24 h. Corresponding values in group 2 infants were 50% and 80%. These data suggest that the priming dose regimen for vecuronium administration may be a useful alternative for rapid-sequence induction for cesarean section when succinylcholine is contraindicated. However, the onset and clinical duration were longer than desired, and the NACS data suggested residual effects in the infants.

Key Words: NEUROMUSCULAR RELAXANTS, VECURONIUM. INDUCTION, ANESTHESIA—rapid sequence.

Succinylcholine remains the muscle relaxant of choice in situations—including cesarean sections—where a rapid-sequence anesthetic induction and intubation are indicated to secure the airway and prevent aspiration of gastric contents. There are clinical situations, however, in which the use of succinylcholine is contraindicated. These include susceptibility to malignant hyperpyrexia, myotonia, plasma cholinesterase deficiency, a variety of neurologic disorders, and sepsis (1). When confronted with a patient with one of these conditions, the obstetrical anesthesiologist must consider the advantages and disadvantages of awake intubation, conduction anesthesia, or an alternative muscle relaxant. Paramount in these considerations is maternal and fetal safety.

Vecuronium, a nondepolarizing muscle relaxant with an intermediate duration of action and minimal hemodynamic side effects, has been reported to be a suitable alternative to succinylcholine for producing muscle relaxation during rapid-sequence induction in nonpregnant patients (2,3). However, such an evaluation has not been formally reported in pregnant patients requiring an operative delivery. In the present studies, to the best of our knowledge the first evaluation of vecuronium as the sole muscle relaxant for patients requiring general anesthesia for cesarean section, we measured neuromuscular blockade, safety, and efficacy of vecuronium when used as an adjunct in rapid-sequence induction in this patient population.

Methods

After approval of the appropriate institutional review committees, a total of 21 consenting parturients at

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term requiring elective cesarean section for obstetrical considerations were enrolled. Each patient received metoclopramide, 10 mg IV 1 h before surgery, and sodium citrate, 30 mL orally immediately before the induction of anesthesia.

After arrival in the operating room, an intravenous catheter was inserted, and a lead II electrocardiograph, automated blood pressure device, pulse oximeter, and neuromuscular blockade monitor were applied. Each patient was assigned on a random basis to one of two dosing regimens of vecuronium.

Neuromuscular blockade was measured by the twitch tension of the adductor pollicis muscle in response to ulnar nerve stimulation at the wrist using surface electrodes. The stimuli were square wave, bipolar, supramaximal current pulses 0.2 ms in duration at a frequency of 0.15 Hz (NeuroStim II, Neuro Technology, Houston, Tex.). Adductor pollicis contraction was measured using an adductor pollicis monitor (Medar Corp., Scarsdale, N.Y.), and recorded on a direct writing oscillograph.

Baseline twitch height was recorded in each patient during a 5-min period of preoxygenation. Before delivery of this single twitch stimulus, the patient was reassured and told she would experience "a tingling sensation in her wrist and a jerk of her thumb."

After the recording of the baseline twitch, the 11 patients randomized to group 1 were given 10 μg/kg vecuronium as a priming dose, followed 4–6 min later by 3–4 mg/kg thiopental and 100 μg/kg vecuronium. Two patients in group 2 received 200 μg/kg vecuronium followed immediately by 3–4 mg/kg thiopental. The remaining eight patients in group 2 received the thiopental first. Drug doses were calculated on the basis of actual body weight.

During induction, cricoid pressure was applied and maintained until intubation of the trachea. Intubation was performed at the time of complete loss of twitch or if there was any decrease in oxygen saturation below 100%. During this time the responses to single twitch stimuli at 1-s intervals were recorded. After intubation, each patient received nitrous oxide (50% inspired) and oxygen with 0.5% halothane until delivery of the fetus. After delivery, anesthesia was maintained with nitrous oxide (70% inspired) and oxygen together with 20 mg morphine IV in increments for supplemental analgesia. During this time, the intensity of neuromuscular blockade was measured every 10 s by the depression of the twitch response from baseline levels.

The time to onset of neuromuscular block was the time between the completion of the injection of vecuronium and 100% twitch suppression. Clinical duration was the interval between the completion of vecuronium administration and return to 25% of the baseline twitch height. At this time, neuromuscular blockade was reversed with the administration of increments of 0.4 mg atropine and 1 mg neostigmine IV.

Time intervals between the first injection of vecuronium and intubation were recorded. Intubating conditions were evaluated using the following scale:

Excellent = jaw relaxed, vocal cords apart and immobile, no diaphragmatic movement;

Good = jaw relaxed, vocal cords apart and immobile, some diaphragmatic movement;

Poor = jaw relaxed, vocal cords moving, "bucking";

Inadequate = jaw not relaxed, vocal cords closed.

Time intervals between the induction of anesthesia and delivery and between uterine incision and delivery were recorded. One-minute and 5-min Apgar scores and neonatal Neurologic and Adaptive Capacity Scores (NACS) (4) at 1 and 24 h after delivery were recorded. In addition, the individual tests of passive and active tone within the overall NACS profile were compared between infants from each maternal treatment group. These values were used to assess further the residual vecuronium effects.

Umbilical cord venous and maternal venous blood samples were obtained at the time of delivery for the determination of vecuronium concentrations. The samples, 8 mL each, were drawn into heparinized tubes containing 2 mL of 1 M $NaHPO_4$ and centrifuged, and the plasma was frozen at −70°C. Vecuronium was measured fluorometrically using the method of Kersten et al. (5). The range of sensitivity for the assay was 20–500 ng/mL vecuronium.

Postoperatively, each patient was questioned about recollections of muscle weakness, respiratory difficulty, etc., before loss of consciousness.

Statistical comparisons were made using Student's *t*-test for all data except the Apgar and NAC scores, which were compared using the Fisher's exact test. Differences were considered statistically significant when $P < 0.05$. The data are reported as mean values ±1 SD.

Results

One mother, randomized to group 1, was replaced in the study because of an equipment malfunction in the recording of the twitch responses. Data from the infant of this mother are included in the data analy-

Table 1. Maternal Mean (± 1 SD) Age, Weight, and Induction to Delivery and Uterine Incision to Delivery Times

	Group 1	Group 2
Age (yr)	26 ± 1	25 ± 1
Weight (kg)	76 ± 4	80 ± 3
I-D time (min)	9 ± 1	11 ± 1
U-D time (s)	71 ± 9	76 ± 14

I-D, induction to delivery; U-D, uterine incision to delivery.

Table 2. Mean (± 1 SD) Times to Onset and Clinical Duration, Time to Tracheal Intubation, and Intubation Scores After Vecuronium

	Group 1	Group 2
Onset (s)	177 ± 21	175 ± 18
Duration (min)	73 ± 10	115 ± 19[a]
Intubation (s)	155 ± 12	156 ± 8
Intubation score		
Excellent	10	9
Good	1	1

[a] $P < 0.001$ with respect to group 1.

Table 3. Mean (± 1 SD) Maternal and Umbilical Venous Plasma Concentrations of Vecuronium, and UV/MV Ratios

	Group 1	Group 2
Maternal (ng/mL)	515 ± 50	838 ± 71
Umbilical (ng/mL)	73 ± 13	107 ± 12
UV/MV ratio (%)	14 ± 3	13 ± 1

MV, maternal venous; UV, umbilical venous.

Table 4. Mean Values for Birth Weight, Apgar and NACS Scores, and NACS Passive and Active Tone

	Group 1	Group 2
Weight (g)	3443 ± 135	3405 ± 50
Apgar (% greater than 7)		
1 min	70	50
5 min	100	90
NACS (% with score of 35–40)		
1 h	50	50
24 h	70	80
Passive tone (% scoring 2)		
Scarf sign	90	90
Elbow recoil	90	100
Popliteal angle	80	80
Lower limb recoil	80	80
Active tone (% scoring 2)		
Neck flexor contraction	60	70
Neck extensor contraction	70	60
Palmar grasp	60	90
Traction response	40	40
Supporting reaction	70	60

One infant included in group 2 had 1- and 5-min Apgar scores of 3 and 8, which we attribute to a induction to delivery time of 21 min. One infant included in group 1 had NACS of 14 and 19 at 1 and 24 h, respectively, which we attribute to unanticipated, multiple congenital anomalies at the time of birth.

sis. Thus, 20 mothers and 21 infants were studied. There were 10 mothers in each group. There were 11 infants from group 1 and 10 from group 2 mothers.

Ages and weights of the mothers in each treatment group were similar. Differences in mean times between induction and delivery (9 ± 1 and 11 ± 1 min) and between uterine incision and delivery (71 ± 9 and 76 ± 14 s) were not statistically significant (Table 1).

The mean time to onset of neuromuscular blockade was 177 ± 21 s in mothers in group 1 and 175 ± 18 s in mothers in group 2 (Table 2). The difference was not statistically significant. In the patients in group 1, the minimum and maximum onset times were 90 and 300 s, respectively, as compared with 120 and 300 s in group 2. The mean times to intubation were 155 ± 12 and 156 ± 8 s in groups 1 and 2. This difference was not significant. In 12 patients (six in each group) twitch suppression was 100% before intubation, and in none of these patients did oxygen saturation decrease. Maternal oxygen saturation decreased below 95% for four patients in each group. The mean time to desaturation was 140 s (range, 100–175) in group 1 and 143 s (range, 115–195) in group 2 (NS). In no patient did saturation decrease below 85%. All patients in whom the oxygen saturation decreased were immediately intubated before complete loss of the twitch response with a prompt return to 100% saturation. Intubating conditions were rated as good (one in each group) or excellent in all 20 patients. Two patients in group 2 recalled muscular weakness before going to sleep. There were no similar recollections in the patients in group 1. The clinical duration of action of vecuronium was 73 ± 10 min in group 1 and 115 ± 19 min in group 2. This difference was statistically significant. Neuromuscular blockade was successfully reversed in all patients.

The mean maternal venous plasma concentration of vecuronium was 515 ± 50 ng/mL in group 1 and 838 ± 71 ng/mL in group 2. The corresponding neonatal concentrations were 73 ± 13 and 107 ± 12 ng/mL, respectively (NS). The difference between the ratio of umbilical venous to maternal venous concentrations (14% and 13% for groups 1 and 2, respectively) was not significant (Table 3).

All newborns were of term gestation (36–41 wk). The birth weights, 1- and 5-min Apgar scores, 1- and 24-h NACS, and passive and active tone NACS profiles between groups are tabulated in Table 4. There were no significant differences in these measurements between groups.

Discussion

At the present time there is no satisfactory alternative to succinylcholine for cesarean section in the parturient in whom this drug is contraindicated. In these rare situations, awake intubation is an option, but may be difficult and unpleasant in the unpremedicated patient. In addition, the use of nerve blocks to obtund airway reflexes is relatively contraindicated in the pregnant patient because of the increased risk of aspiration. Regional anesthesia is the preferred alternative technique, but in the event of inadequate anesthesia, intravascular injection of local anesthetic, or excessively high levels of epidural or spinal anesthesia, airway control may also require the use of a muscle relaxant drug. In addition, in the presence of conditions associated with potential or actual fetal distress, including placental abruption, umbilical cord prolapse, or severe pregnancy-induced hypertension with coagulopathy, use of regional anesthesia may be precluded. As a third alternative, there is the use of vecuronium for intubation, an option that has the advantage of minimal cardiovascular side effects (6), little or no histamine release (7), and minimal placental transfer of the drug (8–10).

Two techniques have been used to shorten the onset time of vecuronium for rapid sequence induction. The priming technique involves use of a smaller "priming" dose of relaxant to cause mild inhibition of neuromuscular function followed by injection of a larger dose of drug to produce rapid augmentation of the neuromuscular block (11). Risks of this technique include the distressing sensation of dyspnea for the patient, respiratory impairment, and possible aspiration of gastric contents (12). Taboada et al. (13) found the optimal doses and interval for the priming dose technique for vecuronium to be 0.01 mg/kg followed in 4 min by 0.1 mg/kg. This sequence induced complete paralysis in 102 s. Alternatively, omitting the priming dose and increasing the definitive dose of vecuronium decreases the time to onset and also produces minimal cardiovascular side effects (14). With doses of 0.20–0.28 mg/kg, onset times are in the range of 64–140 s (2,15). The longer times to onset measured in the present studies may reflect pregnancy-induced alterations in vecuronium pharmacokinetics.

The present study compared both the priming- and high-dose treatment techniques for vecuronium administration in rapid-sequence induction for cesarean section. The results demonstrated no differences in times to onset or intubating conditions. Times to complete twitch suppression were just under 3 min, and the intubating conditions were good to excellent in both groups of patients studied. Interestingly, intubating conditions were the same even when patients were intubated before the onset of complete blockade of the twitch response. These results are consistent with the study of Agoston et al. (16), in which intubating conditions were good with only 50% neuromuscular blockade providing that the block developed rapidly. This is attributed to the dense innervation and excellent perfusion of the diaphragm and larynx (17).

No patient given a priming dose of vecuronium (group 1) experienced dyspnea or anxiety during the 4–6-min interval between receiving the first dose of vecuronium and the induction of anesthesia. Two patients in the high-dose group (group 2) recalled chest heaviness or dyspnea after receiving vecuronium. These responses were attributable to the fact that our initial protocol had been to administer the vecuronium in group 2 patients before thiopental, and that during the induction of anesthesia in these two patients there was a 10–15-s delay between the administration of vecuronium and thiopental. It was our impression that the symptoms in these patients were the result of a rapid onset of neuromuscular blockade consequent to the higher dose used. At that time our protocol was changed so that thiopental was given before vecuronium. The symptoms noted are consistent with the observations of Bencini and Newton (18) who found that, when using vecuronium, respiratory inadequacy occurs when twitch height is suppressed only 20%–30%. The two patients in the present study were immediately anesthetized and intubated, and developed neither desaturation nor dysrhythmias. As the result of these observations, we believe that thiopental should precede or immediately follow high-dose vecuronium to prevent maternal discomfort and the possibility of aspiration due to an unprotected airway.

Four patients in each group, in the present study, had a decrease in oxygen saturation to 95% or less approximately 140 s after the injection of thiopental and before complete loss of the twitch response. When this reduction in oxygen saturation occurred, the patients were immediately intubated. In each instance the intubating conditions were excellent and there was rapid recovery of maternal saturation. We attribute the ease of intubation in these patients to the fact that instrumentation is possible with 50% neuromuscular blockade (16).

The clinical duration of vecuronium was significantly different between the two groups. As shown in Tables 1 and 2, clinical duration far exceeded operative time in the patients given high-dose vecuronium, and was also prolonged, although to a lesser extent, in those given priming doses. In clinical practice, however, reversal of neuromuscular blockade can be accomplished well before 25% return of twitch height. These observations expand the results of a previous report that the total duration of vecuronium-induced neuromuscular blockade increases linearly with the dose used, and that neuromuscular blockade is easily reversed in all patients when there is a 25% return of twitch height (13).

Previous studies have reported the use of vecuronium, 0.04–0.1 mg/kg, in patients undergoing cesarean section after succinylcholine administration for intubation (8–10). Two of these (8,10) reported that the umbilical venous to maternal venous blood ratio for vecuronium was approximately 11% and that there were no adverse neonatal effects. The relatively low placental transfer of vecuronium helps assure that the quantity of drug redistributed to the fetus will be pharmacologically inconsequential. The maternal venous/umbilical cord venous ratios of 14% and 13%, respectively, for the priming- and high-dose vecuronium techniques used by us are consistent with the previously reported results, despite the fact that we used doses three to five times greater. It is important that the maternal and neonatal blood levels were correspondingly higher in our patients as a result of the higher vecuronium doses that we used. A legitimate question is whether these higher levels are cause for concern with respect to the neuromuscular function of the newborn infant. In adults the plasma concentration of vecuronium causing 50% twitch depression is 94 ng/mL during nitrous oxide-halothane anesthesia (19). In neonates, the plasma concentration of *d*-tubocurare required to produce 50% neuromuscular blockade is one-third that in adults under similar anesthesia (20). That is, neonates are more sensitive to *d*-tubocurare. Assuming that the pharmacodynamics of vecuronium is similar to that of *d*-tubocurare, the mean plasma levels of 73 and 107 ng/mL vecuronium measured by us in infants in the priming- and high-dose groups, respectively, when compared with the 94 ng/mL value reported as effecting 50% twitch depression (20), may reflect clinically significant blood levels. We have evidence that both refutes and supports this conclusion. First, there were no significant differences between the two groups of neonates in terms of Apgar scores, total NACS, or specific NACS test items of active and passive tone, as shown in Table 4. Second, only 50% of infants in either group achieved a NACS of 35–40 at 1 h, a range of values described by Dailey et al. (10) as denoting a vigorous infant. At 24 h, 30% of the infants of mothers given priming doses of vecuronium and 20% of the infants of mothers given a single large dose had not achieved a score of 35–40. These data suggest that there were residual, neuromuscular effects of vecuronium. However, mothers of the infants as well as the nursing personnel caring for the neonates reported no problems with feeding or other behaviors. These observations suggest that if residual neuromuscular effects of vecuronium were present, they were not clinically significant. Dailey et al. (10) reported that umbilical cord arterial blood levels for vecuronium are lower than umbilical venous levels, indicating that the relaxant is redistributed or metabolized by the infant. Unfortunately, we were unable to obtain umbilical arterial samples in the present study. Had this been possible, data might have been obtained to help clarify the relevance of the measured umbilical venous vecuronium plasma levels. All in all, however, our observations may indicate residual vecuronium effects in the neonates studied.

Our study may be criticized in that the NACS evaluations should have been performed by a single individual who was blinded to the maternal treatment. In addition, we did not include a control cesarean section population that received succinylcholine for tracheal intubation.

In summary, we conclude that vecuronium may be useful as an alternative drug in the rapid-sequence induction of patients for cesarean section when succinylcholine is contraindicated. With and without priming doses of vecuronium, it was possible to intubate under good to excellent conditions even before loss of the twitch response. Neither dosing technique provided a more rapid onset of action, and both the time to onset and clinical duration were longer than desired. Although there were no differences in Apgar scores between the two groups, and no clinical evidence of vecuronium effects in either group of neonates, the NACS data suggested that subtle residual effects may have been present. Finally, because the intubating conditions were equally satisfactory, maternal duration of action shorter, and neonatal blood levels 30% lower, we recommend the priming-dose technique be used when giving vecuronium to parturients requiring cesarean section.

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Clinical Reports

Delayed Recognition of Podophyllum Toxicity in a Patient Receiving Epidural Morphine

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Key Words: TOXICITY, PODOPHYLLUM. ANESTHETIC TECHNIQUES, EPIDURAL—morphine.

Podophyllum is frequently used by both dermatologists and gynecologists for the treatment of condylomata acuminata. However, the potential toxicity of topically applied podophyllum is not widely appreciated. We describe below a postanesthetic death directly related to topically applied podophyllum; diagnosis and treatment may have been delayed because early symptoms of podophyllum toxicity were incorrectly attributed to epidural morphine, which we had administered for postoperative pain control.

Case Report

A previously healthy, 17-yr-old, 73-kg woman came to the operating room for CO_2 laser ablation of massive vulvovaginal condylomata acuminata; there was a superficial 3 × 6-cm fungating lesion as well as multiple lesions of the vagina and cervix. She had no known medical problems, allergies, or previous anesthetics, and was taking oral antibiotics in preparation for the surgical procedure. We planned to use lumbar epidural anesthesia during surgery and to administer epidural morphine to control postoperative pain.

After inserting an epidural catheter at the L3-4 interspace and verifying that tests for intravenous and subarachnoid catheter placement were negative, we administered a total of 20 mL of 1.5% lidocaine with epinephrine 1:200,000 via the epidural catheter; this resulted in a T-4 level of surgical anesthesia, without any evidence of circulatory or respiratory compromise. After 1 h of laser fulguration, it appeared that the amount of bleeding, scarring, and tissue damage that might be caused by continued use of the laser would be substantial; therefore, the surgeon believed that the remaining lesions would be best treated with topical podophyllum. The surgeon applied 90 mL of 17.5% podophyllum in tincture of benzoin to the remaining condylomata, and covered the treated areas with gauze dressings. When the patient arrived in the recovery room, we administered preservative-free morphine, 5 mg, through the epidural catheter to provide postoperative analgesia. Two hours after surgery, the patient had normal sensory and motor function of her lower extremities, and she returned to her room in satisfactory condition. Postoperative orders included hourly counts of respiratory rates as well as specific treatments for pruritus and nausea.

Four hours postoperatively, the patient experienced an episode of nausea and vomiting, which resolved without medical intervention and was believed to be a side effect of the epidural opioid. Thirteen hours postoperatively, the patient developed a low-grade fever (38°C), mild tachycardia (100 beats/min), and tachypnea (40 breaths/min). Her blood pressure remained stable (120/88 mm Hg), and she denied any discomfort; the symptoms were attributed to inflammation or infection at the site of surgery. Three hours later (16 h postoperatively) the patient was unrousable. Her pupils were small but

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reactive to light and there was no response to painful stimulation. The upper and lower extremities were flaccid, and deep tendon reflexes were minimal. The patient's heart rate was 110 beats/min, her blood pressure was 110/70 mm Hg, her temperature had increased to 40.0°C, and she continued to breathe deeply at a rate of 40 breaths/min. Because of presumed sepsis, the surgeon obtained blood cultures and began antibiotic therapy.

Despite the persistent tachypnea, both the nurses and the surgical house officer caring for the patient believed that the patient's unresponsiveness might be related to the epidural morphine. Therefore, they administered 0.2 mg naloxone intravenously, which had no effect on the patient's clinical status. An arterial blood sample obtained while the patient breathed room air revealed a pH of 7.39, Pa_{CO_2} of 34 mm Hg, Pa_{O_2} of 49 mm Hg, and HCO_3^- of 20.2 mEq/L. A blood count was markedly abnormal: there were 40,600 WBC/mm^3, including 18% bands, 6% metamyelocytes, and 11% myelocytes. Although the hemoglobin concentration was 13.9 g/dL, many of the red blood cells appeared misshapen, suggesting a toxic hematologic event. There were also marked elevations in serum creatinine phosphokinase (1524 U/L, normal <188 U/L), lactic dehydrogenase (1470 U/L, normal <150 U/L), and serum glutamic oxaloacetic transaminase (141 U/L, normal <30 U/L) activities; serum glutamic pyruvic transaminase was mildly elevated (36 U/L, normal <25 U/L). After removal of the epidural catheter, diagnostic lumbar puncture revealed clear cerebrospinal fluid (CSF) with normal opening pressures, slightly elevated protein (62 mg/dL), and slightly decreased glucose (47 mg/dL) concentrations. Cultures of CSF, blood, urine, and the epidural catheter tip were negative. Chest x-rays taken during the next 8 h revealed worsening noncardiogenic pulmonary edema, suggestive of a neurogenic, toxic, or infectious etiology.

In view of the rapidly progressing neurologic symptoms and the large amount of podophyllum that was still in contact with the patient's skin, we considered the likelihood of podophyllum toxicity. Therefore, we washed the remaining podophyllum off of the vulvar region and began supportive therapy including tracheal intubation, positive pressure ventilation, and intravenous hydration. During the next several hours, the patient's clinical status continued to deteriorate; she became oliguric (the urine tested 2+ for protein, and the sediment contained many red blood cells). Despite 150 mEq of intravenous sodium bicarbonate, the patient's arterial pH decreased to 7.22, the Pa_{CO_2} was 43 mm Hg, and the bicarbonate level was 17.4 mEq/L. There was also a large alveolar-arterial O_2 gradient; with an F_{IO_2} of 0.8 and PEEP of 5 cm H_2O, the Pa_{O_2} was only 210 mm Hg.

In an attempt to remove circulating podophyllum from the patient's bloodstream, we began hemoperfusion through a Amberlite resin canister. Shortly after this was started, however, the patient became hypotensive. A pulmonary artery catheter, inserted to clarify the etiology of this hypotension, revealed pulmonary artery pressures of 26/18 mm Hg and a wedge pressure of 6 mm Hg; because of the patient's hemodynamic instability, cardiac output was not determined. After intravenous fluid administration, resin hemoperfusion was attempted once again; this time the patient became hypotensive and developed an idioventricular bradycardia. She could not be resuscitated despite treatment with multiple vasopressors and inotropic agents, as well as the insertion of a transthoracic pacemaker; death occurred 26 h postoperatively.

Discussion

Podophyllum, a resin mixture obtained from the dried rhizome and roots of *Podophyllum peltatum* (May apple), has been widely used as a popular remedy for constipation since its accidental discovery 125 yr ago (1). In 1942, Kaplan reported on the use of topical podophyllum resin for treating anogenital verrucae as well as condylomata acuminata (2).

Although there have been several reports of fatal toxicity after ingestion of podophyllum (3–5), there is only one previous death reported after topical application of this drug (6). Although multiple organ systems may be affected, podophyllum seems to exert its major toxic effects on the nervous system. Central nervous system effects of podophyllum include changes in sensorium, confusion, hallucinations, seizures, and coma; patients may also develop ataxia, hypotonia, areflexia, and autonomic neuropathy. The most common peripheral nervous system effect is a generalized sensorimotor polyneuropathy that may resolve slowly over weeks to months (7,8). There may also be elevated protein in the CSF (7).

Among the early signs and symptoms of podophyllum toxicity, after both ingestion and topical application, are abdominal pain, nausea, and vomiting; symptoms usually begin between 4 and 13 h after podophyllum administration (4). In our patient, abdominal pain may have been masked by the epidural morphine that she had received approximately 4 h earlier; both the analgesia and side effects of epidural morphine would be expected to be greatest at about this time (9). Our patient's nausea, vomiting, and mental status changes were attributed to the epidural morphine; however, in retrospect, they may well have been early signs of podophyllum toxicity.

Autonomic dysfunction, including tachycardia and hypotension (supine or orthostatic), consistently develops in patients with podophyllum toxicity (8); other common findings include leukocytosis with left shift, elevated liver enzyme levels (10), oliguria (4,6), and hematuria (8). The fact that our patient developed all of these abnormalities strongly suggests that she had absorbed a toxic amount of podophyllum.

Podophyllotoxin, a potent cytotoxin that interferes with the function of intracellular microtubular structures, is believed to be responsible for the toxicity of podophyllum resin. It binds to tubulin in the mitotic spindle, disrupting mitosis (11). Podophyllotoxin also seems to disrupt axoplasmic flow by binding to microtubular proteins (12); this may explain the neurologic deficits associated with podophyllum toxicity.

To limit the risks associated with topical application of podophyllum, the total dose should be limited to 2 mL of a 10% solution (in tincture of benzoin) (13). Podophyllum should not be applied to bleeding or friable mucosa or to healthy skin or mucosa; petroleum jelly should be applied around each lesion to prevent unintended contact with these tissues. Finally, the compound should be meticulously removed by washing with soap and water within 4–6 h after application (14). Because of its potential teratogenicity (15), podophyllum should be used with caution during pregnancy.

If podophyllum toxicity is suspected, initial therapy should be directed at decreasing additional absorption of the agent. When the drug has been applied topically, it should be removed immediately; after oral ingestion, induced emesis, gastrointestinal lavage, and oral administration of activated charcoal may all be effective (4). Once absorption has occurred, the therapeutic alternatives are limited. Because it is lipid soluble, podophyllotoxin is not removed by hemodialysis; however, limited animal data and clinical experience suggest that resin hemoperfusion may be effective (16).

Fatal toxicity may follow the use of podophyllum for treatment of condylomata acuminata. One should maintain a high index of suspicion that vague gastrointestinal or neurologic symptoms could be early signs of toxicity from podophyllum absorption. Analgesic techniques such as epidural morphine, which may mimic the signs and symptoms of podophyllum toxicity and delay diagnosis, should therefore be avoided; small doses of systemic analgesics might be a more appropriate choice.

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Vancomycin Enhances the Neuromuscular Blockade of Vecuronium

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Kentaro Tsueda, MD

Key Words: ANTIBIOTICS, VANCOMYCIN.

Vancomycin is frequently used as the antibiotic of choice for methicillin-resistant staphylococcal infections and *Streptococcus viridans* endocarditis, and as a prophylactic antibiotic in patients with prosthetic heart valves or ventriculoperitoneal shunts (1–4). Adverse reactions to vancomycin include renal toxicity, ototoxicity, cardiovascular depression, histamine release, anaphylactoid reactions, and rare cases of cardiac arrest (5–16). Currently, renal toxicity is considered to be of little clinical significance in patients with normal renal function, but the other side effects of vancomycin are serious. We report a depression of neuromuscular function that developed after intravenously administered vancomycin, something that has not been described previously in the literature.

Case Report

A 21-yr-old woman, 152 cm tall and weighing 34 kg, with recurrent pelvic inflammatory disease and a persistent right adnexal mass was anesthetized for exploratory laparoscopy. This patient had undergone surgery for a posterior fossa neuroblastoma at the age of 2 yr. A ventriculoperitoneal shunt was inserted at that time; it was revised at age 17 yr. The patient had been taking phenytoin for the control of seizures. She had done well since that time except for mild ataxia and mild mental retardation. The patient denied use of tobacco, alcohol, or drugs. There were no known allergies. At the time of surgery, physical examination was normal except for an old scar from ventriculoperitoneal shunt surgery; blood pressure was 100/60 mm Hg and heart rate was 80 beats/min; the patient was afebrile; chest roentgenogram was normal; hemoglobin was 14.5 g% and plasma electrolyte levels were normal; serum phenytoin level was 9.0 mg%.

Anesthesia was induced with 350 mg thiopental and 50 μg fentanyl. Tracheal intubation was facilitated with 4 mg vecuronium. Anesthesia was maintained with 50% nitrous oxide and 0.4%–1% isoflurane. Blood pressure, electrocardiogram, inspired oxygen concentration, oxygen saturation, end-tidal CO_2, and esophageal temperature were monitored. Electromyographic (EMG) response to electrical stimulation of ulnar nerve (train-of-four) was monitored by NMT-221 (Puritan Bennett Corporation, Kansas City, Mo.). A program written in Quick Basic 4.5 (Microsoft, Inc., Redmond, Wash.) received the data from the NMT monitor and displayed the EMG response to the first stimulus (T1) and the response to the fourth stimulus (T4) as two separate bar graphs on an IBM enhanced graphics display. All data were saved as a text file.

Twenty minutes after induction of anesthesia, T1 had returned to 35% of the preinduction level, but T4 was barely perceptible. An infusion of vancomycin (1 g diluted in 250 mL of normal saline) was started at the request of the surgeon. The T1 decreased immediately after the start of the infusion to less than 10% of the preinduction level. T4 was totally absent. The infusion lasted 35 min. Twenty-five minutes after the infusion was started, a blood sample was drawn to determine the level of vancomycin; it was 70 μg/mL. A decrease in blood pressure or heart rate was not observed. Within 3 min of cessation of vancomycin, the EMG began to recover steadily. Twenty minutes later the operation was completed and vecuronium was reversed with 0.6 mg atropine and 35 mg edrophonium intravenously. Initially, the EMG response demonstrated the recovery of the neuromuscular function to near preinduction levels, but the responses decreased approximately 5 min later to the same level they were before the edrophonium was given. The patient was

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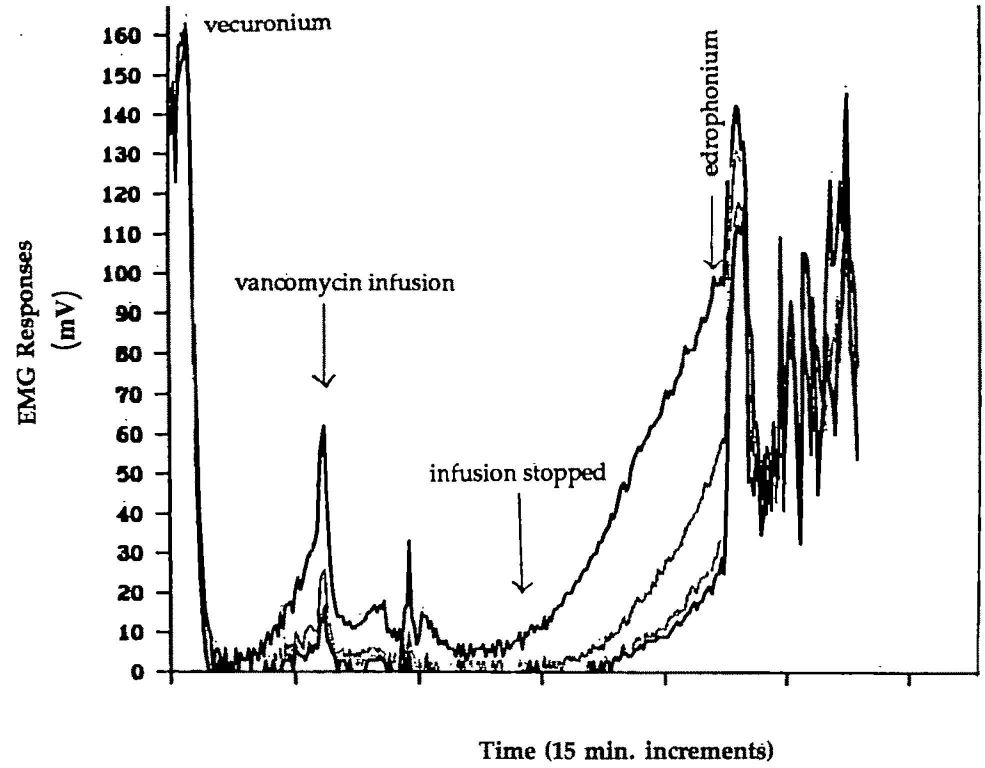

Figure 1. Integrated EMG response to electrical stimulation of ulnar nerve (train-of-four) during vancomycin infusion. T1, *top line*; T4, *bottom line*.

awake and breathing spontaneously but was not able to sustain headlift. The plot of T1 through T4 for the entire period is shown in Figure 1. Twenty minutes after injection of edrophonium the patient's muscle tone was judged to be adequate by both clinical assessment and EMG. The endotracheal tube was removed. The patient's vital signs were stable, and no other side effects were noted.

Discussion

A number of antibiotics, particularly the aminoglycosides, have been shown to produce skeletal muscle paralysis. The available literature suggests that antibiotics have multiple sites of action, i.e., prejunctional structures, postjunctional cholinergic receptors, and muscle membranes (17–20). The response to anticholinesterase and Ca^{2+} of the neuromuscular blockade produced by these antibiotics is variable. Vancomycin, a complex tricyclic glycopeptide, previously has not been considered to affect neuromuscular function (21).

In our patient, the integrated EMG response to electrical stimulation of the ulnar nerve recovered to 35% of the control level approximately 25 min after an intubating dose of vecuronium. The duration of muscle relaxation was that expected in subjects with normal hepatic function. The prompt reduction in the EMG response and the beginning of its recovery coincided with the start and cessation of vancomycin infusion, suggesting that the enhancement of muscle relaxation was caused by vancomycin. The ineffective antagonism by anticholinesterase observed in this patient was also consistent with that which characterizes neuromuscular depression secondary to antibiotics. A substantial depression before and a recovery of T3 and T4 after the administration of edrophonium appear to suggest that vancomycin had an effect on the neuromuscular junction as well as on skeletal muscles.

The effect of antibiotics on neuromuscular function is more likely to become evident during anesthesia than in the absence of anesthesia because depression of neuromuscular function secondary to anesthetic and muscle relaxant drugs is already present. However, there have been no reports of vancomycin-induced neuromuscular depression with the exception of a communication by Glicklich and Figura (22) describing transient apnea and hypotension after an inadvertent rapid infusion of vancomycin, 1 g over 2 min, during peritoneal dialysis. Muscle weakness produced by vancomycin was thought to be the cause of the apnea in this patient. Lack of clinical reports may be partly due to our current practice to infuse vancomycin slowly and to control ventilation during anesthesia. The trachea was intubated in nine of 13 patients previously reported in whom hypotension and/or cardiac arrest developed after the administration of vancomycin (6–10,13–15). However, in a few of these patients in whom the trachea was not intubated, neuromuscular blockade in addition to cardiovascular depression cannot be excluded as an etiologic factor (12,14).

The recommended usual daily intravenous dose of vancomycin in adults is 2 g, 500 mg every 6 h or 1 g every 12 h, with each dose infused over a period of 30 min or, more recently, over 60 min. The safe and effective serum levels have been considered arbitrarily to be 40–10 μg/mL (23) or 50–20 μg/mL (24). The highest concentration of vancomycin is expected to occur at the end of the infusion (25). Thus, the peak concentration in our patient would have been in excess of 70 μg/mL, presumably due to the small size of our patient. The neuromuscular depression in our patient may have been due to the high serum concentration of vancomycin, but this level of concentration can occur during treatment of patients with vancomycin (26).

The experience with this patient suggests that vancomycin in clinically encountered serum concentrations may depress neuromuscular function, especially during anesthesia in which muscle relaxants are used. The recommended dosage and method of administration should be adhered to, with appropriate adjustments for body size and renal function. In addition, patients must be observed carefully throughout anesthesia for signs of neuromuscular as well as cardiovascular depression because adverse effects, although usually associated with large doses or rapid infusion, have also been reported to occur during slow infusion (6,8,9,15).

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Long Thoracic Nerve Block

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Key Words: ANESTHETIC TECHNIQUES, REGIONAL—long thoracic nerve block.

Seven patients with intractable pain of the lateral chest wall under the axilla appeared to have pain originating from spasm of the serratus anterior muscle. A long thoracic nerve block to interrupt selectively the innervation to this muscle could confirm this diagnosis, but a review of the literature revealed no previous reports of this type of block. After reviewing the anatomy, a technique for long thoracic nerve block was developed.

Methods

Anatomy

The long thoracic nerve arises from the anterior branches of the C5, C6, and C7 nerve roots and rarely (8%) from C8 (1). This nerve usually innervates a single muscle, the serratus anterior. It provides no cutaneous innervation. As described by Horwitz and Tocantins (1), the first two roots enter the middle scalene muscle, unite, and join the C7 root. The long thoracic nerve then descends dorsally to the brachial plexus and down the anterolateral aspect of the chest wall (2). It sends branches to all the digitations of the serratus anterior muscle (2). In some instances (5%) the root from C5 may course independently of the others to be distributed to the upper digitations of the serratus anterior (1). Other anatomic variations include those in which the C7 root (8%) is absent or unites with the C5 and C6 roots below the clavicle (13%) (1).

Technique

The patient is placed in the supine position without a pillow and instructed to raise his or her head to facilitate palpation of the sternocleidomastoid muscle by making it more prominent. After palpation of the posterior border of the sternocleidomastoid muscle with the index finger, the patient is instructed to lower the head and to relax the neck muscles. The index and middle fingers of the anesthesiologist's palpating hand are then rolled laterally to identify the anterior scalene muscle, the interscalene groove, and the middle scalene muscle. The index and middle fingers are then placed on the middle scalene muscle and a 22-gauge 3-cm regional block needle (short bevel) attached to a nerve stimulator is slowly advanced into the muscle in a direction that parallels the long axis of the middle scalene muscle, in a direction that is caudad and slightly lateral (Figure 1). The muscle is entered just above the level of C6, which is determined by noting the level of the cricoid cartilage. The lateral chest wall over the serratus anterior muscle is exposed to observe muscle contractions, and, in addition, an assistant attempts to identify contractions induced with the nerve stimulator by placing his hand over the area of the muscle. If contraction of the trapezius muscle occurs, indicating stimulation of the spinal accessory nerve, the needle is redirected more anteriorly to locate the long thoracic nerve. The final needle position is maintained at the point where maximum contraction of the serratus anterior muscle is noted. After negative aspiration, 5 mL of local anesthetic solution (0.5% bupivacaine) is injected.

To evaluate the motor effect of the block, the strength of the serratus anterior muscle should be evaluated before and after the block. One function of the serratus anterior is to connect the third, fourth, and fifth ribs with the vertebral border of the scapula and draw the scapula forward (3). When muscle function is impaired, the vertebral border of the scapula protrudes dorsomedially, the shoulder

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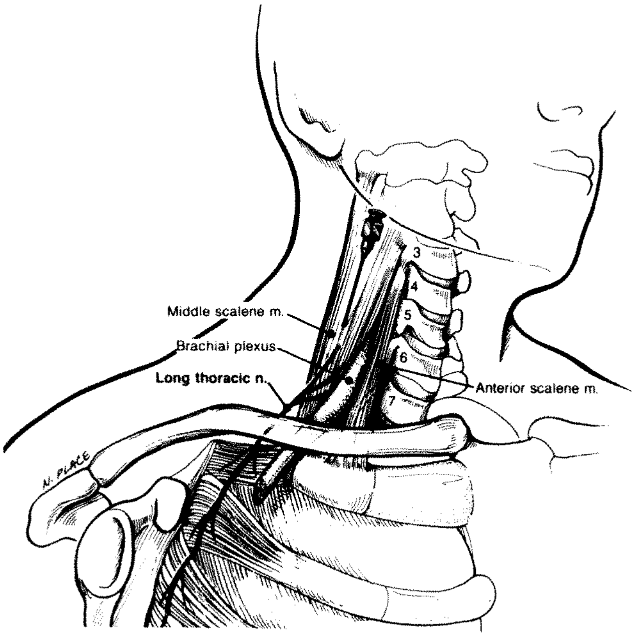

Figure 1. The long thoracic nerve, which innervates the serratus anterior muscle, is blocked as it pierces the middle scalene muscle.

droops, and the arm cannot be abducted beyond 90° (4). The protrusion of the scapula is referred to as scapular "winging" and is accentuated when the arm is pressed against a wall and an attempt is made to push the body away from the wall (4).

When the block is performed to relieve muscular spasm, gentle stretching exercises also should be given to the patient in an attempt to prevent return of the spasm.

Report of Seven Cases

A 36-yr-old man presented with the complaint of pain in the right lateral chest wall under the axilla after a twisting, pulling injury to the muscle. Chest x-ray after the injury revealed no rib fractures. He had received physical therapy, multiple trigger point injections, and intercostal nerve injections, including neurolytic intercostal blocks. Each of these treatments resulted in only partial relief of his pain, and thus relief was only temporary (several hours to less than a week). On physical examination good strength of the serratus anterior muscle was noted as well as hypesthesia over the painful area due to the previous neurolytic intercostal blocks. The pain appeared to be originating from the serratus anterior muscle and to be due to spasm of that muscle. It was believed that a block of the long thoracic nerve could help establish the diagnosis because the long thoracic nerve is the sole innervation of consequence of this muscle. The above technique was developed and utilized in this patient.

The patient was examined by a physical therapist before and after the block. Although no weakness of the serratus anterior muscle was present before the block, pronounced scapular winging was present at 30 min after the block. Also, at 30 min after the block the patient reported complete relief of pain, which he had described as severe before the block. He was instructed in a home program of gentle stretching exercises for the serratus anterior muscle. On follow-up, the patient reported no return of pain for 1 mo. After 1 mo, however, the pain gradually returned until at 1.5 mo, the pain had returned to the original level.

The block was subsequently performed in six patients with confusing pain problems, all with pain below the axilla on the chest wall. Motor block of the serratus anterior was confirmed after the block in each patient by the presence of scapular winging. Electromyography was also utilized in two patients to further document that the block effectively interrupted innervation of the serratus anterior muscle. Before the block, normal motor unit activity was noted on electromyography. After the block, voluntary motor unit activity was abolished, indicating motor block. Of the six patients in which the block was utilized, four had excellent pain relief, suggesting that most or all of their pain originated from the serratus anterior muscle. These patients had pain relief that outlasted the effective duration of action of the local anesthetic. One patient reported only partial pain relief, but it was believed that her pain was more diffuse, originating not only from the serratus anterior muscle but also from other adjacent structures. The one patient who reported no pain relief from the block had had a thoracotomy, and subsequent injection of local anesthetic into his thoracotomy scar resulted in good pain relief.

The only complications that were seen from the block were hypesthesia in the cutaneous distribution of branches of the cervical plexus. In all seven patients, hypesthesia was noted in the cutaneous distribution of the supraclavicular nerves, and in two patients hypesthesia in the distribution of the lesser and greater occipital nerves was noted.

Discussion

The technique described for blocking the long thoracic nerve is relatively simple and safe. It provides a useful diagnostic and therapeutic block of the serratus anterior muscle. Although the necessity to block this muscle may arise only infrequently, there are select patients, such as the ones we described, for whom knowledge of this technique may prove extremely beneficial.

It should be noted that even though we have described the long thoracic nerve solely as a motor nerve, it may also transmit sensory information from its muscular innervation, the serratus anterior. This may help to explain its usefulness in the relief of pain originating from spasm of this muscle.

We had few complications associated with this block. We did note block of branches of the superficial cervical plexus, which lie under the posterior border of the sternocleidomastoid muscle. The use of a smaller volume of local anesthetic may decrease the likelihood of block of these nerves. Although not noted in our patients, local anesthetic spread resulting in block of the dorsal scapular nerve (innervator of rhomboids and levator scapula) and the spinal accessory nerve (innervator of the sternocleidomastoid and trapezius) may also be possible in view of their close proximity to the long thoracic nerve.

Anatomic variations in which the C5 root courses independently into the muscle or in which the C7 root joins the nerve below the clavicle may lead to only partial block, if the local anesthetic does not spread to these roots. Even partial block, however, may be beneficial in the relief of pain from muscular spasm.

Knowledge of the relationship between the long thoracic nerve and brachial plexus roots may be helpful in performing a brachial plexus block. If the serratus anterior is stimulated in an attempt to locate the brachial plexus trunks (subclavian perivascular block) or roots (interscalene block), the needle should be redirected more anteriorly. Likewise, if during performance of a long thoracic nerve block the brachial plexus is stimulated, the needle should be redirected more dorsally to locate the long thoracic nerve.

In conclusion, no previous reports are available for block of the long thoracic nerve, and the technique that we have described is relatively simple and associated with few complications.

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Letters to the Editor

A Controllable Suctioning Laryngoscope

Key Words: EQUIPMENT, LARYNGOSCOPE—suctioning.

To the Editor:

Profuse oral secretions, oropharyngeal bleeding, and regurgitation can block the view of the anesthesiologist and require the anesthesiologist to alternate between suctioning and laryngoscoping the patient. An assistant may be needed to continuously suction while the anesthesiologist attempts intubation. To solve this problem, I have developed a device (Figure 1) consisting of a suctioning tube welded to the blade of the laryngoscope.

The external diameter of the suctioning tube is 2.5 mm and the internal diameter is 1.75 mm. The tube has a hub in its proximal end, and there is a port on its superior surface. The hub is angled such that the thumb of the hand holding the laryngoscope can be placed conveniently over the port and the amount of suctioning can be controlled. This leaves the other hand free to intubate. This also saves valuable time.

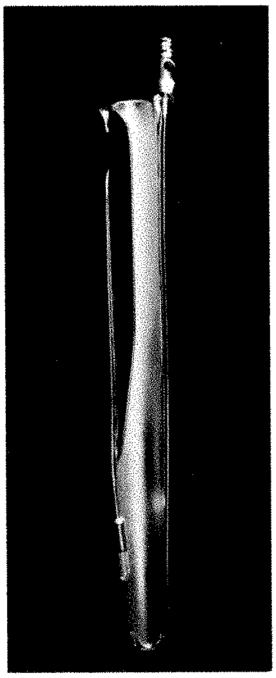

Figure 1. A laryngoscope blade showing the suctioning device incorporated into it.

The author acknowledges the help of Mr. A. Salerno of Anesthesia Medical Specialties in Santa Fe Springs, California, for making the refined model of the blade.

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Microcatheters for Continuous Spinal Anesthesia

Key Words: ANESTHETIC TECHNIQUES, SPINAL—continuous.

To the Editor:

I read with interest the report of Drs. Hurley and Lambert describing their experience with a microcatheter for continuous spinal anesthesia (1). I have recently tried this technique myself, and confirm the advantages which they list in their discussion.

However, their incidence of catheter breakage appears to be alarmingly high (2/58 patients). I have had the same problem myself using a 27-gauge catheter (Preferred Medical), which snapped during removal after a 7-h orthopedic operation with very satisfactory anesthesia with lidocaine. Resistance was experienced during attempted removal, and this persisted despite varying the degree of flexion and extension of the back. The catheter stretched and finally snapped, leaving 5–6 cm within the patient. After neurosurgical consultation, the situation was explained to the patient, and an expectant course followed.

There have been few reported cases of sheared intraspinal catheters (2–4), although the subject is discussed at length by Bromage (5). His recommendation is to inform

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the patient and not to attempt surgical removal. This seems sensible, but there is a paucity of published reports on the subject. Is an intrathecal catheter fragment as innocuous as is claimed for epidural or extraspinal location (4)? Our neurosurgeon's opinion was that this may not be so, but—perhaps fortunately—the catheter fragment could not be visualized radiographically or by computed tomography scan.

I am not aware of published data comparing the relative tensile strengths of the microcatheters available at this time. It may be unwise to promote microcatheter techniques for wide application when the catheters available are so fragile and the potential for morbidity associated with breakage is unknown. There is clearly a need for a stronger microcatheter to facilitate acceptance of an otherwise excellent technique.

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To the Editor:

Hurley and Lambert recently described their pioneering experience with a 32-gauge spinal catheter (1). Their effort to devise a microcatheter for use through a 26-gauge needle represents a logical attempt to provide the benefits of spinal anesthesia to young patients while simultaneously reducing their risk of postdural puncture headache (PDPH). But is this merely a technical tour de force or does it represent a real clinical advance?

Denny and colleagues (2) reported an incidence of PDPH approximating 1% utilizing an 18-gauge Hustead needle and a 20-gauge catheter. They attribute this low incidence of PDPH to well-defined factors. In each case, the spinal needle bevel was positioned parallel to the dural fibers in an attempt to cut as few of them as possible. Such precautions are associated with a decreased incidence of PDPH (3). Furthermore, the presence of a catheter that traverses the dural hole initiates an inflammatory response at the dural hole margins (4). This inflammatory tissue is thought to speed repair of the hole and thereby help to prevent PDPH.

Postdural puncture headache is easily and successfully treated in more than 90% of cases. Therefore, a 1% incidence of this complication is clinically acceptable. Conventional wisdom would predict a smaller incidence of PDPH associated with a 26-gauge needle and a 32-gauge catheter than that associated with an 18-gauge needle and a 20-gauge catheter. Nevertheless, the potential benefit of a small decrease in PDPH incidence, compared to a 10% probability of inability to thread the microcatheter, detracts from its clinical utility and renders this system undesirable in its present form.

General acceptance of a 32-gauge catheter will require demonstration of overwhelming superiority with regard to PDPH in the young adult, obstetric, and ambulatory populations as well as an improved design, one that overcomes its present high incidence of inability to thread the catheter.

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In Response:

We appreciate the concerns of Drs. Baxter and Reed regarding the possibility of catheter breakage and the risk of PDPH after continuous spinal anesthesia.

In response to Dr. Baxter, we agree that a catheter breakage rate of 2/58 is too high. We would like to point out, however, that both of these events occurred during development of the 32-gauge catheter and do not apply to current commercially available MicroSpinal catheters (Rüsch Inc., Duluth, Ga.). The first break occurred in phase 1, where the 32-gauge polyimide tubing did not contain a reinforcing stylet (break strength = 0.7 lb, Table 1). The second break occurred during phase 3, when a stainless steel stylet was in place but not bonded to the polyimide tubing as is now the case with the commercial product. Furthermore, this latter case occurred under unusual circumstances, as described in our article (1).

Table 1 shows the break strength and elongation characteristics of the three currently available spinal catheters, the 32-gauge polyimide tubing without reinforcing stylet and two epidural catheters. Clearly, the strength of the polyimide tubing alone is inadequate for clinical use. Whereas the 32-gauge polyimide catheter with bonded stainless steel reinforcement has greater tensile strength, the larger 27-gauge polyurethane and 28-gauge nylon spinal catheters show greater elongation before breaking. We firmly believe and hasten to point out that all currently

Table 1. Break Strength and Elongation Characteristics of Currently Available Spinal Catheters[a]

Manufacturer	Catheter material	Gauge	Break strength (lb)	Elongation (%)
TFX/Rüsch	Teflon	20	3.0	280
TFX/Rüsch	Nylon	20	3.9	290
Preferred medical[b]	Polyurethane	27	1.3	475
Kendall[c]	Nylon	28	1.3	550
TFX/Rüsch[d]	Polyimide/stainless steel	32	2.6	1, 100[e]
	Unreinforced polyimide tubing	32	0.7	100

[a] Testing done with standard Instron tensile strength equipment by Teleflex Medical, Jaffrey, N.H.
[b] Catalog No. 901, Lot 903127.
[c] Catalog No. 5423, Lot HU8305KG.
[d] Catalog No. 13005-32, Lot 909007.
[e] Stylet elongates 1%, polyimide elongates 100%.

Table 2. Incidence of Headache With Continuous Spinal Anesthesia

Author	Reference No.	Year	Needle gauge	% Headache
Denny	2	1987	18	1
Giuffrida	3	1972	20, 21	16
Hurley	1	1990	26	4
Cohen	4	1989	17	20
Gold	5	1989	18	12
Culling	6	1989	18	22

available clinical catheters have the potential for breaking and *must always* be handled carefully. This is especially true for the smaller diameter catheters. Extra care is indicated when moving patients with these catheters in place and during their removal.

In response to Dr. Reed's suggestion that "smaller is not necessarily better," we believe that all the data may not be in concerning the incidence of headache when large needles and catheters are used for continuous spinal anesthesia. In Denny's (2) report of 117 patients, the one PDPH occurred, not surprisingly, in a young patient (29-yr-old man). The average age of the patients in that study was 63 yr with only 33% of patients less than 60 yr of age. Denny's (2) low incidence of PDPH has not been confirmed by other investigators. Giuffrida et al. (3) reported an incidence of 16% using 20–21-gauge needles in patients aged 17–45 yr (mean, 30 yr) given continuous spinal anesthesia. Cohen et al. (4) found a 20% incidence of PDPH in parturients who had an accidental dural puncture with 17-gauge needles during attempted epidural anesthesia that was then converted to continuous spinal anesthesia. Gold et al. (5) observed a 12% incidence of PDPH in ambulatory patients above the age of 50 yr given continuous spinal anesthesia with conventional epidural catheters inserted through an 18-gauge Tuohy needle. Similarly, Culling et al. (6) reported a 22% incidence of PDPH in general surgical patients undergoing continuous spinal anesthesia with large-diameter needles and epidural catheters. The mean age of the patients who developed PDPH in this study was 63 yr. These data (Table 2) suggest that PDPH after continuous spinal anesthesia is directly related to the size of the needle used to insert the catheter.

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To the Editor:

We read with interest the report by Hurley and Lambert concerning their experience with a microcatheter continuous spinal anesthesia technique (1). They remark that "low doses of local anesthetic intermittently injected virtually eliminate the possibility of systemic toxic reactions." We recently encountered, however, a case that strongly suggested the occurrence of a systemic toxic reaction to intrathecal lidocaine.

Our patient was a 70-yr-old woman with diabetes mellitus and peripheral vascular disease to whom we gave continuous spinal anesthesia for femoral artery-popliteal artery bypass surgery. Regular medications included captopril, verapamil, insulin, digoxin, and pentoxifylline. Intrathecal lidocaine (225 mg; total 3.1 mg/kg) was administered over 150 min, at which time the patient began to complain of nausea (without vomiting) and a "swimming sensation." Her sensorium was clear, and her sensory level was at T-10; she denied pain and tinnitus; her blood pressure and heart rate were stable and normal for the patient; urine output was >70 mL/h, serum glucose was 237 mg/dL, and arterial blood gas tensions were within normal limits. Sedation was limited to 0.25 mg midazolam 2 h before the complaint.

As did Hurley and Lambert, we considered lidocaine toxicity unlikely; nevertheless, we discontinued the lidocaine and began maintenance of anesthesia with tetracaine. Seventy-five minutes afterward, the patient reported progressive resolution of her uncomfortable sensations. Unfortunately, we did not obtain a serum lidocaine level. The resolution of her symptoms with the discontinuance of intrathecal lidocaine, along with the elimination of other probable causes of our patient's dysphoria, lead us to conclude that this patient was experiencing a mild systemic toxic reaction to lidocaine placed intrathecally.

Hurley and Lambert also mention the "potential for catheter breakage," and discuss their two instances of broken catheters. We have had occasion to place intrathecal catheters, often in older people with calcifications of the supraspinous and interspinous ligaments or limitations of flexibility of the lumbar spine. By using the *paramedian* approach described by Bridenbaugh and Greene (2) we have never encountered the "impassibility" through ligaments that can make spinal anesthesia in older patients difficult. More important, we have never encountered difficulty in removal of a catheter, difficulty that may otherwise occur when the patient arches his or her back. We expect the paramedian approach to become the technique of choice when using any of the small catheters coming on the market.

Complications of continuous spinal anesthesia will undoubtedly continue to come to light, but we believe the advantages of the technique will expand its popularity.

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Hidden Costs of Disposables: Is Color Coding Desirable?

Key Words: EQUIPMENT, DISPOSABLE. ECONOMICS, EQUIPMENT—disposable.

To the Editor:

Medical devices labeled for single use are increasingly used in all areas of medicine especially in the operating room. It is estimated that approximately 5% of the total hospital budget or 9% of the nonsalary part of it is spent in procuring these products.

In deciding whether the use of a disposable is advantageous, the following should be determined:

1. Is the disposable product as good as or better than the nondisposable item it will replace?
2. What are the economical considerations?
   (a) How does the price of the single-use product compare with the nondisposable item?
   (b) How many times can the nondisposable be safely reused? Can the nondisposable item be repaired and at what price?
   (c) What are the costs of cleaning and/or sterilizing the alternative reusable item?
   (d) What are the costs of stocking the disposables, reordering, distribution, bookkeeping, etc.?
3. What is the environmental impact?

It is not always easy to answer these questions. For example, if cleaning is performed by already available personnel, and no additional people need to be hired, this factor is negligible. All too frequently, cleaning time is measured and a cost calculated that in reality does not exist.

There are, however, several other factors that we presently do not take into consideration, but that will in the future become more important. Most disposables, for example, are made of plastics that require oil for their production. The oil supply is not unlimited and also makes us depend on imports from other, not always friendly, nations.

Also, many plastics are not biodegradable and may be around many centuries from now. In more densely populated areas, disposing of garbage has become increasingly difficult, and space has become an extremely valuable commodity. In a university hospital it is said that each bed generates over 6 tons of trash yearly. To make things worse, a large percentage of medical disposables are considered contaminated waste and are no longer accepted in already overloaded landfill sites. Transportation to faraway sites or local incineration (which by itself is becoming unfeasible in many regions) have been the only alternatives—costly ones.

Because many disposables are made of plastic, an attitude has developed that anything made of plastic should be discarded after a single use. Costly nondisposable articles are not recognized as such and disappear in the trash together with the disposable materials. In this way the cost of medical care is, however indirectly, increased by the introduction of disposables. Anyone in charge of operating room and anesthesia supplies is well aware of this phenomenon.

The above indicates why we must be more conscious of the consequences when we decide to use disposable equipment. The following points are to be considered:

1. Is there a real need for the disposable product? Nobody has shown, for example, that disposable anesthesia circuits are of any importance in prevention of crossinfection. In an institution providing 20,000 anesthetics a

year, the cost for these systems amounts to more than $100,000 a year.

2. Is the disposable product biodegradable, not in vitro, but in reality after being buried a meter under the surface in a landfill?
3. Many disposables could be reused if cleaning and resterilization are simple and straightforward. Manufacturers, understandably, have not been anxious to cooperate, but there is no reason why some disposables could not be reused a number of times.

I propose the following. Disposables that cannot be reused should be color-coded so hospital personnel as well those managing disposal facilities can easily recognize them as such. I suggest that potentially infective disposables such as syringes and needles be colored bright orange. This may prevent accidental contamination. Disposable materials unlikely to be infective could be colored bright yellow. Thus, nondisposable equipment could be readily recognized by the lack of coloring and not inadvertently thrown away and destroyed. To be of value, such a measure must be universally accepted by the industry. It will be less costly if it is introduced on a voluntary basis for a number of years before becoming mandatory.

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Acromegaly and Radial Artery Cannulation

Key Words: ARTERIES, RADIAL—cannulation.

To the Editor:

It has been suggested that cannulation of the radial artery in patients with acromegaly may be potentially hazardous on the basis that, theoretically, hypertrophy of the transverse carpal ligament, resulting from the acromegalic process, may result in carpal tunnel syndrome and may cause external compression of the ulnar artery thereby compromising blood flow to the hand (1). This is difficult to understand because the ulnar artery is located outside of the carpal tunnel (2). In addition, the article originally proposing a risk associated with radial artery catheterization was based on a study of 10 acromegalic patients, three with neurologic symptoms consistent with carpal tunnel syndrome (1). In these three and in two additional patients, Allen's test demonstrated impairment of ulnar artery circulation in either one or both hands. For unspecified reasons, in three of these five patients a radial artery catheter was not inserted. No ischemic complications were observed in the seven acromegalic patients in whom radial artery catheters were placed. It is difficult to discern how these data support the thesis that radial artery catheterization is dangerous in acromegalic patients.

Subsequent to this report, Slogoff et al. demonstrated that the Allen's test is not predictive of ischemic damage after radial artery cannulation (3). It appears that the initial concern raised was based on a test without predictive value. This is consistent with the experience at our institution regarding the use of radial artery catheters in acromegalic patients.

We retrospectively reviewed the anesthetic records and postoperative daily progress notes of all acromegalic patients who underwent transphenoidal resection of a pituitary adenoma at the Mayo Clinic from January 1985 to December 1989. It is not part of our anesthetic practice to perform an Allen's test before placement of a radial artery catheter. An indwelling radial artery catheter was placed in 51 patients. There were no ischemic complications. These findings suggest that placement of radial artery catheters in acromegalic patients is not hazardous as previously suggested.

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A Simple Pediatric Arm or Leg Protector

Key Words: ANESTHESIA, PEDIATRIC—leg protector. EQUIPMENT, EXTREMITY PROTECTOR.

To the Editor:

The anesthesiologist's primary responsibility is to protect the patient. This goal includes protection of a patient's intravenous line(s) and monitors (blood pressure cuffs, pulse oximeter) from mechanical interference.

Arm shields are commercially available to provide this protection in adults. To our knowledge, however, no device has been readily available to guard the limbs of infants or children against mechanical pressure, especially when their limbs are hidden from the anesthesiologist's view by surgical drapes, etc. We therefore describe the fashioning of such a device from readily available materials.

Acrylic plastic becomes softened when heated uniformly to 120°C; 0.32-cm-thick clear acrylic sheeting was therefore made to appropriate dimensions by scoring the sheeting and cutting it out. This cut-out piece is heated in an oven on a flat surface. When warm it is "draped" over a wooden

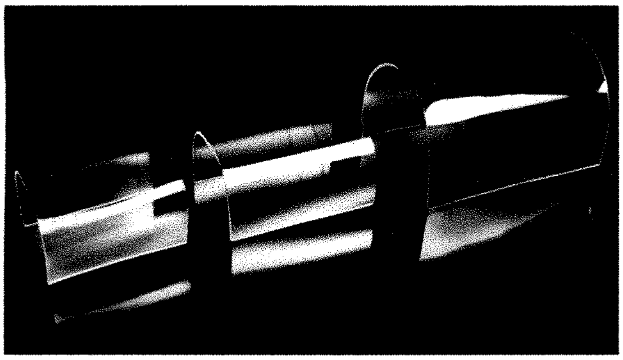

Figure 1. Acrylic pediatric arm or leg protectors of various sizes.

block as high and at least as long as the device intended. This block should, however, be narrower than the protector planned, and should be placed on a hard, flat surface. The two long edges of the softened plastic sheet are molded by hand (with appropriate protection) against the flat surface to assure parallel edges when cooled. Cooling and hardening take place rapidly. Sharp edges can be made dull with sandpaper.

Three such protectors are shown in Figure 1. We have used these devices, in various sizes, for premature infants and for children up to 5 yr of age. That the protector is transparent increases one's confidence that no part of the child's limb is being compressed. Taping the device to the table mattress is adequate to prevent tipping over of the protector; most "hostile" forces are downward. We have been quite satisfied with the degree of protection afforded the patients' limbs, intravenous sites, and monitoring devices.

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Preoperative H_2-Receptor Antagonists

Key Words: GASTROINTESTINAL TRACT, STOMACH—antacids.

To the Editor:

I read with great interest the report by Lehot et al. suggesting that preoperative administration of H_2-receptor antagonists may lead to postoperative pneumonia (1).

Several points must be made regarding this study and the practice of "prophylactic" administration of H_2-receptor antagonists.

Although the authors correctly point out that the sample size was too small, their self-criticism concerning the P-value of 0.06 is unwarranted. The use of 0.05 is an arbitrary convention that in modern medical literature confers uncontestable validity on all results with $P < 0.05$ and condemns to obscurity any results unfortunate enough to have $P > 0.05$. One should not consider a study invalid simply because the P-value did not attain the sacred value. Is a study invalid simply because the probability of a type I error was estimated at 5% rather than 6%? I suspect that is why the authors toned down their language, calling the results a "trend." If the results are not significant there is no trend, so that does not circumvent the problem. The larger problems—not addressed—were as follows:

1. Group 3 patients, whose intragastric pH values were no different from group 1, developed more postoperative pneumonias. How do the authors explain the differences in gastric colonization and postoperative infection when the groups did not differ in pH?
2. The study was compromised by the uncontrolled postoperative adjustment of intragastric pH by different methods. If the hypothesis to be tested was the effect of preoperative dosing, all patients should have received the same postoperative antacid therapy. On the other hand, if the effects of *perioperative* antacid therapy were being tested, the patients should have continued on the same regimen throughout the perioperative period.

As the authors note, Laws et al. documented the dramatic changes in gastric flora that occur after preoperative administration of H_2-receptor antagonists (2). In subsequent correspondence, it was suggested that one may be exchanging the aspiration of acid for aspiration of colonized gastric contents (3). There are no clinical data to suggest that preoperative administration of H_2-receptor antagonists decreases the incidence or severity of aspiration of gastric contents—such practices are based on speculation and extrapolation from animal data. The value of the present report by Lehot and colleagues is that it alerts the anesthesia community to the possibility that preoperative pH adjustment of intragastric contents is not without danger.

The unrestrained enthusiasm with which many centers sprinkle H_2-receptor antagonists over their patients like holy water is reminiscent of the (now-defunct) practice of administering antacid suspensions to parturients (4). How many women were subjected to this untested regimen before data became available suggesting that the prophylaxis was as bad as the disease (5–7)?

Preoperative pH adjustment of intragastric contents should not be blanket therapy. It should be given to patients deemed to be at increased risk for aspiration, when the neutralization of gastric acid is considered more important than the risk of gastric colonization. If such therapy is undertaken, adjustment of gastric pH should occur as close to the time of induction as possible to decrease the amount of gastric colonization. Such coverage may be obtained by the use of clear liquid oral antacids (the onset of action of which is essentially immediate) and H_2-receptor antagonists in liquid form (given either intravenously, intramuscularly, or orally), which have a faster onset (8).

Perhaps Polonius' advice regarding friendship applies to medical fads as well:

Those friends thou hast, and their adoption tried,
Grapple them unto thy soul with hoops of steel,
But do not dull thy palm with entertainment
Of each new-hatch'd, unfledged courage.
(*Hamlet*, Act I, Sc. 3)

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In Response:

As Dr. Gorback points out, the *P*-value of 5% is used arbitrarily in statistics. However, the probability of a type I error with a *P*-value of 6% found in this clinical study is great enough to call for a new study with more patients.

Consequently, in group 3, the number of postoperative pneumonias was not *statistically* greater than in group 1. Similarly, there were significantly more patients in group 1 than in group 2 with a sterile gastric juice ($P < 0.01$), but the difference was not significant between groups 1 and 3, so that ranitidine, but not gastrozepine, enhanced gastric colonization when given before surgery.

The aim of this study was to assess the influence of *preoperative* regimen on *intraoperative* gastric pH and colonization. Thus, the postoperative regimen was not controlled. However, the number of patients given antacids and H_2-receptor antagonists postoperatively was roughly the same in each group, which may suggest that the main difference between the three groups was the preoperative regimen. A different study, one using a controlled *perioperative* regimen, would be of great interest in determining the number of postoperative pneumonias.

We agree entirely with Dr. Gorback's recommendation that treatments that neutralize gastric acid be given only in selected cases and immediately before induction of anesthesia to avoid gastric colonization.

As for Polonius' advice, we are not sure we understand Shakespeare's English very well. However, as premedication with diazepam, and anesthesia with high dose fentanyl and diazepam, can be associated with intraoperative gastric pH values as high as 5 or 6, the administration of ranitidine or gastrozepine before cardiac surgery does not seem necessary and may be hazardous. A saying in Molière's language tells us that "The best is the enemy of the good."

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Cardiac Cycle and Synchronous Left Hemidiaphragmatic Contraction

Key Words: MUSCLE, SKELETAL—diaphragm contractions.

To the Editor:

Abnormalities of diaphragmatic function in the perioperative period can produce diagnostic and therapeutic challenges to the physician. Abnormalities include diaphragmatic paralysis (1), disordered movement after upper abdominal surgery (2), hiccup (3), diaphragmatic flutter (4), and diaphragmatic contraction synchronous with cardiac contraction (5). "Diaphragmatic flutter" is the term for irregular contractions of the diaphragm associated with epigastric or chest pain, shortness of breath, and discomfort. We observed left hemidiaphragm synchronously contracting with each cardiac cycle in three patients in the perioperative period.

One of the patients was a 16-yr-old boy with recurrent coarctation of aorta after initial repair as an infant. Induction of anesthesia was with thiopental (5 mg/kg) followed by atropine (20 μg/kg). Succinylcholine (2 mg/kg) was used for muscle relaxation for tracheal intubation. Isoflurane and nitrous oxide in oxygen were used for maintenance of anesthesia. As the patient recovered from the effects of succinylcholine, we observed marked movement of the left precordium and left hypochondrium. A marked hyperdynamic circulatory state, an abdominal aortic aneurysm, and vascular malformation of spleen were excluded from our differential diagnosis. Careful examination revealed that the left hemidiaphragm was contracting with each cardiac cycle. We tried to record the spontaneous action potentials from the surface of the chest but had technical difficulties. Administration of 0.1 mg/kg vecuronium intravenously abolished the abnormal diaphragmatic contraction. Anesthesia and surgery were uneventful thereafter.

Another patient was a 9-yr-old girl with complex myopathy and complete heart block with a permanent pacemaker that had been implanted by thoracotomy in the past. The present surgery was for tendon lengthening in the lower limbs. After thiopental induction of anesthesia (5 mg/kg IV), atracurium (0.3 mg/kg IV) was used for muscle relaxation to facilitate tracheal intubation. Anesthesia was then maintained with isoflurane and nitrous oxide in oxygen. At the end of the surgery the atracurium-induced muscle relaxation was reversed with physostigmine (50 μg/kg) and atropine (20 μg/kg), and isoflurane was discontinued. We observed at this time that the left hemidiaphragm was contracting synchronously with each cardiac cycle. As the level of anesthesia lightened and the patient started breathing spontaneously, the diaphragmatic contractions disappeared.

The third patient was a 10-mo-old infant who had uneventful repair of his ventricular septal defect during cardiopulmonary bypass. When continuous positive airway pressure was initiated during weaning from the ventilatory support on the second postoperative day, we noted that when the patient was asleep the left hemidiaphragm contracted with each heart beat, a phenomenon that lasted for 15 min. When the child became vigorous and began actively breathing, the contractions disappeared.

There are some common factors in these three patients. The left hemidiaphragmatic contraction with heart beat was transient and occurred in patients who had past or recent thoracotomy and were anesthetized or sedated with a relaxed abdominal wall. Fluoroscopy or electromyographic recordings were not possible due to the transient nature of the disorder. There are very few reports about this phenomenon in the literature (5). Anesthesiologists should be aware of this type of diaphragmatic disorder. The clinical significance and the mechanism of the disorder are not known at the present time.

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Lidocaine Intoxication During General Anesthesia

Key Words: ANESTHETICS, LOCAL—lidocaine toxicity.

To the Editor:

Convulsions may be one of the first manifestations of overdoses of local anesthetics in both animals and humans. However, although high concentrations of inhalation anesthetics have been shown in animal studies (1) to prevent convulsions and to enhance lethal effects of local anesthetics, probably due to their depressive effects on the cardiac and respiratory functions, the effects in humans of overdosage of local anesthetics combined with inhalation anesthetics have not been described. We present here a clinical case of intravenous lidocaine overdosage during halothane and nitrous oxide anesthesia manifested by circulatory collapse and cardiac arrhythmias.

A 57-yr-old woman (height, 150 cm; weight, 50 kg) with rheumatoid arthritis was scheduled for total elbow replacement. Although suffering from mild myasthenia gravis, she had been taking no medication and had been in a fairly good state of health. Her blood pressure (BP) was 130/80 mm Hg and her electrocardiogram was normal with a sinus rhythm at a rate of 80 beats/min. After administration of hydroxyzine (25 mg IM) and atropine (0.5 mg IM), as premedication, anesthesia was induced with 50 mg thiopental followed by nitrous oxide (67%) and halothane (3%) in oxygen by face mask. The trachea was intubated 1 min after lidocaine was given intravenously for prevention of coughing (2) in what was thought to be a dose of 2 mg/kg but what was subsequently found to be a dose of 20 mg/kg. Immediately after intubation, BP decreased from 110/70 to 60/20 mm Hg with the onset of a supraventricular tachyarrhythmia at a rate of 130 beats/min. The pupils were widely dilated, and the light and cough reflexes were absent. Anesthesia was discontinued, and 100% oxygen was administered. She was placed in a head-down position. Arterial blood gas tensions were in the expected range except for a mild metabolic acidosis. Two minutes later, systolic BP decreased further to 40 mm Hg, and etilefrin (ethylphenylephrine) (5 mg IV) was given as an antihypotensive. Blood pressure increased to 80/40 mm Hg and thereafter continued to increase gradually. Ten minutes after the intravenous administration of lidocaine generalized convulsions started, but disappeared soon after administration of diazepam (5 mg IV). At that time, the anesthetist noticed that a large amount of lidocaine (20 mg/kg) had been administered as a single bolus injection 1 min before intubation. Additional diazepam (10 mg IV) was administered. Twenty minutes after the intravenous administration of lidocaine a sample of arterial blood had a plasma concentration of lidocaine measured by fluorescence polarization immunoassay of 10 μg/mL. Thirty minutes after the lidocaine injection, the patient began to breathe spontaneously and after another 20 min, i.e., 50 min after the lidocaine was given, she recovered consciousness, at which time her plasma lidocaine level was 8.5 μg/mL. The operation was postponed. The tracheal tube was removed when the plasma lidocaine level reached 6.5 μg/mL. In the recovery room, the patient was fully alert and suffered no sequelae. Three weeks later, she underwent the operation uneventfully with the same anesthetic regimen, except the dose of lidocaine was 2 mg/kg IV.

In an animal study (3), we found that subconvulsive doses of intravenous lidocaine depressed cardiovascular function in a dose-dependent manner during 1%–1.5% halothane–nitrous oxide anesthesia combined due, in all probability, to decreased sympathetic activity and direct myocardial depression. In the present case, circulatory collapse and severe cardiac arrhythmia occurred soon after the intravenous injection of 20 mg/kg lidocaine during halothane–nitrous oxide anesthesia. Convulsions did not appear until the anesthesia was lightened. Bromage et al. (4) reported the minimum blood concentration of lidocaine at which toxic manifestations, including convulsions, occurred in humans to be about 10 μg/mL during light nitrous oxide–thiopental anesthesia. In our patient, because the plasma lidocaine level was 10 μg/mL 20 min after the lidocaine injection, it is probable that blood concentrations in excess of 10 μg/mL, i.e., a toxic level, lasted for 20 min. We suggest that convulsions induced by lidocaine even at very large dosages do not occur in humans or animals during deep inhalation anesthesia. Cardiovascular collapse and severe cardiac arrhythmias may be the first important signs of lidocaine intoxication during deep inhalation anesthesia.

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Analysis of Pentothal Confirms Decreased Potency

Key Words: ANESTHETICS, INTRAVENOUS—thiopental.

To the Editor:

After noting that several patients seemed unusually "light" after an appropriate dose of thiopental (Pentothal), we submitted two partially empty syringes to Abbott Laboratories, manufacturer of thiopental under the trade name of Pentothal, for their analysis of drug content.

The analysis revealed the contents of the syringes had potencies of 75.2% and 73.6% of the active ingredient in the syringes. Abbott's Medical Director, Dr. Callan, states in his letter, "Aside from some error in reconstituting the product, the values suggest an underfilled Pentothal powder vial." He also states that thiopental as a "hydroscopic compound . . . challenges the manufacturing efficiencies during the filling process and because of associated technical considerations, a vial on a rare occasion may be inadequately filled and escape detection."

What is puzzling is that we had administered 4–5 mg/kg Pentothal as a bolus to initiate induction. Seventy-five percent of that amount should still render a patient unconscious and relaxed, especially when used with a narcotic and muscle relaxant. It did not. One 67-yr-old opened his eyes and weakly grabbed the anesthesiologist's hand after laryngoscopy. He developed tachycardia, hypertension, and transient ST segment changes that resolved with the addition of an inhalational agent. Another patient squirmed vigorously on the table during the induction after using a different syringe of Pentothal from the same lot. In all instances, the manufacturer's directions were carefully followed in aspirating sterile water into the Pentothal powder-filled syringe.

Explanations for this phenomenon besides less than fully potent Pentothal are just as worrisome. Careless mixing of the bacteriostatic sterile water supplied by Abbott (we have noted an extra 1–3 mL of water per vial) could decrease potency. Undetected drug use/abuse as well as suspect potency of other anesthetic adjuvants could also explain the above.

Have others experienced the same problem that we did?

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Postspinal Headache

Key Words: ANESTHETIC TECHNIQUES, SPINAL—headache.

To the Editor:

The lessened incidence of postspinal headache in older middle-aged patients is attributed by Stone and DiFazio (1) to pressure build-up in the leaked cerebrospinal fluid as a result of the relatively closed state of epidural space. I believe a somewhat simpler explanation is now available.

At autopsy of elderly persons, the dura mater presents as an unelastic sheath of relatively dense connective tissue.

At autopsy of infants, in contrast, the spinal dura is distinctly elastic; spontaneous retraction of the cut edges after transverse incision in situ reveals that the dura mater is under cranio-caudal tension, and longitudinal incision indicates that tension in the transverse direction is also present. These observations imply that a puncture in the spinal dura will be less likely to gape and leak cerebrospinal fluid in the elderly than in the young.

In this connection it may be interesting that aging skin loses elasticity (2) and develops wrinkles. Owners of a deeply lined face can console themselves with the thought that they may be correspondingly immune from post-lumbar puncture headache.

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Bronchial Cuff Pressure of Endobronchial Double-Lumen Tubes

Key Words: ANESTHETIC TECHNIQUES, ENDOBRONCHIAL—cuff pressure. EQUIPMENT, TUBES—endobronchial.

To the Editor:

Brodsky et al. (1) describe an interesting experimental study concerning the pressure generated by the bronchial cuff of double-lumen endobronchial tubes (DLTs). We had earlier performed a clinical study (2) on this same subject. However, the reviewers and the editor of the journal we had submitted the study to requested that we consolidate some of the data and present our findings in the format of a letter to the editor. As a result some data had to be omitted, as observed by Brodsky et al. (1). I would like to take this opportunity to clear up any doubts that may still remain about this previous study (2). In it, bronchial cuff pressures were compared in left polyvinylchloride (PVC) DLTs manufactured by Mallinckrodt (Bronch-Cath) and in Rusch red rubber Carlens DLTs. In 22 female patients we used 37F DLTs, 11 of each type. We intubated 28 male patients with 39F and 41F DLTs. In 13 we used red rubber DLTs, in 11 39F and in two 41F. In the 15 remaining patients we used PVC DLTs, 11 being 39F and four 41F. The bronchial cuffs were inflated slowly until no air leakage was observed in a beaker of water, as described previously (3).

Although the mean ± SD values for bronchial cuff volume measured in the PVC DLTs (2.95 ± 1.87 mL) were slightly greater than in red rubber DLTs (2.21 ± 1.13 mL), there were no significant differences (Student's unpaired *t*-test). Our volume findings were similar to those described by Brodsky et al. (1) for Robertshaw and Sheridan DLTs. Nevertheless, as previously stated (2), bronchial cuff pressures in PVC DLTs were approximately 2.3 times less than those in red rubber DLTs. We believe, as did Brodsky et al., that the uneveness of the bronchial cuff inflation—which is easily observed, especially in older red rubber DLTs—might explain the difference in the pressure measurements.

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Too Eger to Use Standard Error?

Key Words: STATISTICS, STANDARD DEVIATION OR ERROR?

To the Editor:

Dr. Eger's article on writing a scientific paper (1) contained much good advice, but he was somewhat cavalier in his discussion of the choice between the standard deviation and the standard error. Altman and Gardner (2) wrote, "Their uses are distinguishable," so it should not, as Eger suggested, be a matter of investigators "preferring" one or the other, a point that Horan raised (3). Eger also wrote that standard errors indicate the likelihood of mean values differing, but actually they enable a calculation of this likelihood, based on the 95% confidence limits on the means (which will be wide if samples are small).

The problem with throwaway remarks by influential people (even though they are fun) is that they, too, are influential, and I would rather Dr. Eger had given a reference to an article that would have instructed readers to use the correct statistic.

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Anatomic Consideration of the Fascia Iliaca Compartment Block

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—lumbar plexus block.

To the Editor:

The recent article by Dalens et al. (1) extols the virtue of the fascia iliaca compartment block technique as "easy, reliable, and provid[ing] a high degree of sensory blockade of the lumbar plexus nerves that supply the thigh using reasonable amounts of local anesthetic." A number of questions need to be answered before the technique can be championed over the conventional 3-in-1 technique advocated by Winnie et al. (2).

Dalens et al. used a mixture of 1% lidocaine with 0.5% bupivacaine, both with 1:200,000 epinephrine. Were equal volumes of these two local anesthetics used in the mixture? The text is unclear in this regard. In addition, the authors state that the volumes of local anesthetic injected were calculated on a weight basis. Children weighing less than 20 kg received 0.7 mL/kg, yet children weighing between 20 and 30 kg were given a fixed dose of 15 mL, 20 mL for those 30–40 kg, 25 mL for those 40–50 kg, and 27.5 mL for those over 50 kg. In the 20–30-kg group, 15 mL may be adequate for a 20-kg child, but is inadequate for a 29-kg child (0.52 mL/kg). In the 30–40-kg group, a 39-kg child would receive only 0.51 mL/kg. A 49-kg child likewise would receive only 0.51 mL/kg; on the basis of 0.7 mL/kg, the dose should be 34.3 mL rather than 25 mL. We believe that the differences in volume may be a major factor in the failure rate recorded by Dalens et al. when using the Winnie technique for the 3-in-1 block. Dalens' technique had a greater likelihood of success because infiltration of a local anesthetic just below the inguinal ligament and just behind the anterior portion of the fascia lata (fascia iliaca is part of the anterior portion of the fascia lata) makes it possible to anesthetize the lateral femoral cutaneous nerve and sensory branches of femoral nerve. As per Dalens et al. in their study, all patients developed good anesthesia in the distribution of femoral nerve, but duration of anesthesia was shorter than in the 3-in-1 block as described by Winnie. This finding is consistent with the hypothesis that sensory branches of femoral nerve and lateral femoral cutaneous nerve were blocked by the Dalens technique. On the other hand, in the 3-in-1 group all of the patients developed a femoral nerve block that was longer in duration. This finding is consistent with the hypothesis that the local anesthetic was deposited under the fascia lata and reached the main femoral nerve before it divided into the sensory and motor branches. Failure to develop a lateral femoral cutaneous nerve block is consistent with the inadequate volume of local anesthetic injected. According to the original article by Winnie, volume is the key to a successful block. Dalens et al. did not indicate whether the block failures were in the high end of the weight groupings; this might explain the failure rate reported. Had the authors taken height as well as weight into account in calculating dosage, they might well have had a higher success rate with the 3-in-1 block.

With regard to the anatomic descriptions, the authors describe a two-"gives" technique for performing the fascia iliaca compartment block. The authors believe the first "give" is felt when the fascia lata is penetrated and the needle is advanced, the second "give" when fascia iliaca is penetrated. This is not supported, however, by the anatomy involved. The anterior portion of the fascia lata is a single sheet formed by the fusion of the three abdominal fasciae. Of these, the most superficial is the deep fascia overlying the aponeurosis of the external oblique (fascia innominata), which passes superficial to the inguinal ligament; the middle one is the transversalis fascia on the inner aspect of the anterior abdominal wall, which passes under the inguinal ligament; the internal one also passes under the inguinal ligament and is the continuation of the iliac fascia (3).

Dalens et al. also state that the genitofemoral nerve runs in along the inner aspect of the fascia iliaca, as shown in their Figure 2B. The position of the genitofemoral nerve inside the fascia iliaca is, however, anatomically incorrect. The genitofemoral nerve pierces the psoas fascia and does not run along the inner fascia iliaca (4). The authors refer to the 3-in-1 block as being successful only when the tip of the needle does not lie within the "perifemoral nerve sheath." After extensive literature search and reviewing anatomy texts (3–5), no such term or anatomic structure was located. At the level at which the 3-in-1 block was performed by Dalens et al., the femoral nerve still rests within the inner fascia iliaca.

Finally, we believe that the distribution of the contrast media in the two x-rays (Figures 4A and 4B in the article by Dalens and associates) was different not because the injections were made into different compartments but instead because distribution was affected by flexion and abduction of the hip (Figure 4B) as compared to the unflexed hip (Figure 4A). When the patient is positioned with the hip flexed, the iliacus muscle and the psoas muscle are relaxed and shortened; the fascial space therefore increases, which accounts for the distribution seen in Figure 4B.

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In Response:

We read with interest and, sometimes, with surprise the comments and criticisms made by Kizelshteyn and Crevecoeur. As written in our paper (1), the anesthetic solution consisted of equal volumes of 1% lidocaine and 0.5% bupivacaine, both with 1:200,000 epinephrine, given on a weight basis. Infants were given comparatively more local anesthetics than older children, as is usual in pediatric practice because these patients have a larger distribution volume of drugs, an increased cardiac output, and thus a higher rate of systemic absorption of drugs. If calculations were made according to the body surface area, doses would have been more similar (per surface unit), whatever the age. However, weight is the only easily available parameter in children and this is why we used it (measurement of height is not easy in infants, and even patient's body area is usually extrapolated from weight).

We agree with the statement that the injected volume is a key factor, as for virtually every block procedure, provided the anesthetic solution is introduced within the appropriate anatomic space. We even believe that larger amounts of local anesthetics would have improved our results, especially in regard to obturator nerve block. However, the hypothesis that block failure might have occurred only in "the high end of the weight grouping" is hardly suggested by our data (and did not occur): because the obturator nerve is closer to the site of the injection used in 3-in-1 than to that used in fascia iliaca compartment block procedures, this nerve should have been blocked more often after Winnie's technique (2) than after our own. In fact, just the opposite occurred: 51 complete failures (and one partial failure) in the 3-in-1 group versus only two (and five partial) failures in the fascia iliaca compartment block group. Some other hypotheses suggested in the letter seem rather unlikely. How could a motor block develop if only "sensory branches of femoral nerve and lateral femoral cutaneous nerve were blocked"? (Remark: the lateral cutaneous nerve is exclusively a sensory nerve.) Why not consider the final concentration of the local anesthetics administered (i.e., 0.5% lidocaine and 0.25% bupivacaine) instead?

The same word "fascia" is applied to anatomic layers that are very different in structure. "The superficial fascia of the thigh, consisting as elsewhere in the limbs of loose areolar tissue containing variable amounts of fat" (3): who can imagine that such a loose tissue can produce a "give" when traversed by a needle? Conversely, "the fascia lata, the deep fascia of the region, so termed because of its wide extent, is thicker in the proximal and lateral parts of the thigh," (3) and the iliac part of the fascia iliaca "thus forms a septum between the inguinal ligament and the hip bone dividing the space into a lateral part, the lacuna musculorum, containing psoas major, iliacus, and the femoral nerve, and a medial part, the lacuna vasculorum, transmitting the femoral vessels" (3). Is it really surprising that both these strong fascias (i.e., fascia lata and fascia iliaca) can be distinctly felt as is the ligamentum flavum (whereas the superficial fascia is not felt) during epidural block?

The comments pertaining to anatomic descriptions are interesting in that confusion may result from the terms used (and there are sometimes discrepancies among well-accepted textbooks of anatomy). Usually, the fascia iliaca is defined (and we included this definition in our paper) as the continuous fascial plane enclosing psoas and iliacus muscles, i.e., consisting mainly of two fascias, the iliacus and the psoas fascias (plus their extensions). Thus, stating that "the genitofemoral nerve pierces the psoas fascia" is not contradictory to the statement that "the genitofemoral nerve runs in along the inner aspect of the fascia iliaca." If the meaning of "fascia iliaca" is restricted to that of "iliacus fascia" as suggested by the letter, why is the genitofemoral nerve the only nerve mentioned as piercing the psoas fascia? What about the obturator nerve? and the femoral nerve?

The concept of a fascial plane allowing a local anesthetic to reach distant nerves has been confirmed recently by a (French) paper (4) providing demonstrative computed tomography scans and showing that (with the authors' technique of 3-in-1 block using a nerve stimulator) "two different unpredictable distributions were found; which were independent of the injected volume." One of these distributions, readily evident on the illustration provided, corresponds exactly to what we call a fascia iliaca compartment block (and the whole fascia iliaca is clearly highlighted by contrast material). This study, in addition to our personal iconography, does not support the hypothesis that the position of the hip may play a significant role in the distribution of anesthesia, especially in the very young (provided, in our opinion, that the hip is at rest). However, further studies may be desirable to fix the problem.

Finally, we would like to comment on the last sentence of the first paragraph. Conceiving multieffective nerve block techniques such as the "3-in-1" block (2) was a great thought. The clinical study supporting this very new concept is, in our opinion (5), basically unquestionable. Thus, 3-in-1 blocks are currently as suitable as when they were reported; what may be questioned is the suggested pathway followed by the anesthetic solution for reaching the three nerves. We believe that Winnie's technique is multieffective only when the local anesthetic is injected below the fascia iliaca (i.e., when a fascia iliaca compartment block is performed); if not, only a femoral nerve block develops. Thus, our technique is basically the same as that of Winnie, the only difference being the more lateral site of injection (to avoid any nerve or vessel damage). Our aims were not to describe a technique that can be "championed over conventional 3-in-1 block," but rather to study the reasons why Winnie's technique fails in a number of patients, and how it is possible to improve the results. We believe that the fascia iliaca is the key factor and that deliberately injecting local anesthetics below the fascia iliaca would result almost constantly in multieffective lumbar plexus nerve blocks.

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The Falling Column: A New Technique for Interpleural Catheter Placement

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interpleural.

To the Editor:

Interpleural catheter placement for analgesia has become a popular technique since its introduction several years ago (1). In the original description a well-lubricated air-filled syringe was attached to the Tuohy needle and the needle advanced until the plunger was pulled forward by the negative interpleural pressure.

At our institution we did not have great success with this technique as it seems to depend too much on a syringe plunger moving with reliably minimal resistance. Our subsequent experience with the loss-of-resistance technique was also disappointing. Squier and colleagues (2) commented on this point as well, saying that they "could not ascertain if our needle was outside the pleural space, within the pleural space, or perhaps within the lung parenchyma as a loss of resistance could place the needle into any of the above." We, too, found a high failure rate with this technique, presumably due to incorrect needle placement.

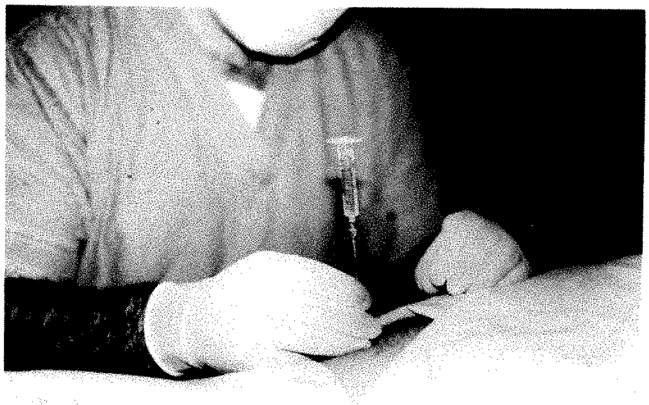

Figure 1. The "falling column" of saline confirms interpleural placement of the needle.

Our solution was a variation of the "hanging drop" technique adapted by Squier et al. On removing the needle stylet we attach to the hub of the Tuohy needle a syringe with the plunger removed. The syringe is then filled with several milliliters of saline, and the needle is advanced. Proper placement is completely unambiguous as the column of fluid is seen to fall away as the saline is pulled into the interpleural space (Figure 1).

A further modification of this approach is to interpose a stopcock between the needle and syringe. This allows one to turn off the stopcock to prevent air entry during the interval between needle placement and catheter placement. By placing the syringe in the stopcock at a 90° angle to the Tuohy needle one can also use this technique in patients in the supine rather than the lateral position.

To date, after use on scores of patients, we have not had a single failure of the technique to achieve a block, nor have we had any instance of clinically significant pneumothorax. We have also found that the clear end point of this technique has facilitated teaching it to our residents.

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Book Reviews

The Practice of Cardiac Anesthesia

Frederick A. Hensley, Jr., and Donald E. Martin, eds.
Boston: Little, Brown and Company, 1990, 750 pp,
$36.50.

The growing body of basic and clinical information in the area of cardiac anesthesia, the multitude of sophisticated pharmacological and technological tools, and the evolving variety of anesthesia and surgical techniques present a welcome challenge to the experienced practitioner. For the young resident, or even the more seasoned anesthesiologist who is infrequently involved in cardiac anesthesia, the abundance of relevant information spread throughout the available literature can be overwhelming. The authors of *The Practice of Cardiac Anesthesia* have presented the latter with a much needed source of complete information and quick reference. This paperback volume is a product of the collaborative effort of 37 contributors from 14 institutions in 24 chapters grouped into three sections.

The first section deals with the general aspects of anesthetic management of patients who present for cardiac surgery and describes all phases of perioperative management from the initial preparation of the anesthesia equipment to the care during the first postoperative 24 h. This section constitutes an all-inclusive condensation of the general elements of cardiac anesthesia discussed in minute, useful detail. However, in their quest for completeness some contributors included certain elementary comments that should be well known even to the novice venturing into the practice of cardiac anesthesia. For example, in the monitoring chapter the reader is informed that "in cardiac anesthesia it is very common to measure pressures within blood vessels directly" and "arterial pressure is often measured by placing a catheter in a peripheral artery." To complete the critical remarks of this otherwise excellent section, a few important inaccuracies and misprints need to be pointed out. On page 12 ("Cyanosis"), the amount of deoxygenated hemoglobin required to produce visible cyanosis is not 5 volumes % as stated but 5 g per 100 mL of blood. On page 64 ("Conversion to miligrams or micrograms per mililiter", Example 3b), 1:1,000,000 is 1 μg/mL and not 1 g/mL as stated. On page 132 all three exponents in the equation for the natural frequency of a pressure transducer system are (−1/2) and not (−2) as stated.

The second section focuses on the management of specific cardiovascular disorders with chapters on myocardial revascularization, valvular and congenital heart disease, cardiac transplantation, thoracic aortic surgery, electrophysiologic disorders, and cardiothoracic emergencies. It offers detailed, clear guidance while avoiding the easy cookbook style. One typographical error in this section merits attention. The dose of PGE_1 in Table 14-3 (page 454) should be expressed in μg/kg/min and not in mg/kg/min. The chapter dealing with electrophysiologic disorders offers a very useful exposition of pacemaker technology and should prove helpful in understanding the technical intricacies and terminology of these highly sophisticated devices.

The final section covers the subject of mechanical support of the circulation. Three chapters are devoted to the mechanical and technical aspects of cardiopulmonary bypass, the pathophysiology of cardiopulmonary bypass, and myocardial preservation. The remaining three chapters deal with circulatory assist devices, extracorporeal membrane oxygenation, and brain protection during cardiac surgery. The chapter on extracorporeal membrane oxygenation focuses on the way in which this treatment modality, still infrequently used elsewhere, is practiced at Pennsylvania State University Medical Center.

The Practice of Cardiac Anesthesia has a number of strengths: (a) it is comprehensive, current, contains a wealth of information, and offers sound practical tips derived from a vast experience in a manner seldom found in standard textbooks; (b) despite the outline format, the writing style makes the reading pleasant and easy; (c) in spite of the inherent dangers of multiauthorship, the editors maintain an even, uniform style and avoid unnecessary repetitions; and (d) the 28-page index is complete.

The value of this fine manual might be enhanced in the following ways: (a) a more complete bibliography could better assist a diligent and curious reader who may want to expand on the knowledge gained from the book; (b) placing page numbers with the outline at the beginning of each chapter, as has been done with the chapter on cardiovascular drugs, would aid in locating a particular item in the text; and (c) using dissimilar fonts to print the multiple levels of headings and subheadings rather than the same bold-face type would reduce confusion and enable the user to consult the manual more efficiently.

The editors' goal was to "provide the reader with a broad-based feel for the way cardiac patients are managed across the country." Unquestionably, they have achieved

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their goal. This nice, well-written handbook will be of great assistance to the residents and fellows in the cardiac operating room or intensive care unit, as well as to the "accomplished practitioners reentering the arena of cardiac anesthesia."

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Drugs and Anesthesia: Pharmacology for Anesthesiologists

M. Wood and A. J. J. Wood, eds. Baltimore: Williams & Wilkins, 1990, 650 pp, $75.00.

The second edition of this text retains the same goal as the first: "To apply a knowledge of the basic principles of pharmacology and pharmacokinetics to anesthesia and to illustrate the importance of these principles to the practicing anesthesiologist." The Drs. Wood wrote most of the material for the book. They were joined by nine other contributors, primarily nonanesthesiologists from institutions in the southeastern United States, who wrote chapters on drugs not commonly described in ordinary anesthesia textbooks.

The book is divided into four sections. The first, covering general pharmacologic principles, is perhaps the best. The field of receptor pharmacology is changing rapidly, and the discussions regarding this area are timely and of great interest. The last three sections covering drugs and anesthesia, cardiovascular therapeutics, and general therapeutics are typical of a pharmacology textbook with a detailed description of a variety of drugs. The book is amply supplied with tables and figures. There are two appendices: one a pediatric dose schedule and the other a listing of pharmacokinetic parameters of important drugs.

This reviewer found the layout to be somewhat confusing and difficult to follow. The legends for figures were not clearly separated from the text. The authors intentionally did not interpose any footnotes in the text to "facilitate readability" and instead, listed them alphabetically at the end of the chapter. If you wish to look up something mentioned in the text you have no idea from which source it originated. Proofreading errors noted in the first chapter alone included substitution of Figure 1.3 for 1.4, a failure to define symbols in Figure 1.7, and a typo in Figure 1.13. The index was generally good although the same page citations were often duplicated after most headings.

The information was mostly current, including a lengthy discussion of propofol. Yet, whereas 12 pages were devoted to halothane and two to methoxyflurane, only five pages were devoted to isoflurane and a half to sevoflurane. Desflurane was not mentioned. Several pages were devoted to a discussion of the newer muscle relaxants, including some not yet released for use in the United States. Chapter 21 included a nice dissertation on the controversial issue of isoflurane and the coronary artery "steal" phenomenon.

The book is exactly as advertised: a pharmacology text for the anesthesiologist. It is a good resource when looking for information about drugs not commonly associated with anesthesia or found in the usual anesthesia textbooks, such as diuretics, prostaglandins, anticoagulants, and drugs acting on the endocrine system. Alternatively, one may wish to buy the book so as to own a basic primer on pharmacology.

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Opioid Analgesia. Volume 14 in Advances in Pain Research and Therapy

Constantino Benedetti, C. Richard Chapman, and Giampiero Giron, eds. New York: Raven Press, 1990, 466 pp, $98.00.

Opioid Analgesia is based on papers presented at the meeting, "Opioid Analgesia: Recent Advances in Systemic Administration," which was held in honor of Dr. John Bonica's 70th birthday in Venice, Italy. This meeting brought together an international panel of basic scientists and clinicians with special interest and expertise in the arena of systemic opioids. The presentations at the meeting were divided into basic science and clinical topics and this format was carried through to the edited volume.

The basic science section of this text is divided into four subsections: (a) historical, (b) basic mechanisms, (c) drug disposition, and (d) controlled intravenous administration. "The History of Opium and Its Derivatives" by Benedetti and Premuda presents the intriguing history of humanity's 4000-year fascination with and use of opium. Ample use of photographs and drawings combined with well-written historical information deserves special mention.

The second subsection, on basic mechanisms, did not seem especially basic given my clinically oriented knowledge of the subject, although some chapters were clearly aimed more at the basic scientist. Neil's chapter describing the biomechanical mechanisms that might explain the clinically encountered syndromes of tolerance and addiction did an excellent job of bridging the gap between basic science and clinical medicine.

The third subsection, on drug disposition, is the best from a clinical point of view. Mather and Stanski's chapter on basic pharmacokinetics presents a concise and quite readable overview of the subject. The authors have avoided relying too heavily on the complex mathematical formulas that have transformed pharmacokinetics from an "art form" into a science, and have chosen instead to emphasize the clinical applications derived from these formulas. This chapter is highly recommended for those seeking a greater understanding of clinically relevant pharmacokinetics and pharmacodynamics of systemic opioids. Inturrisi's chapter, "Effects of Other Drugs and Pathologic States on Opioid Disposition and Response," complements the former chapter nicely.

The fourth subsection, on controlled intravenous administrations, consists of chapters on pharmacokinetic-pharmacodynamic models and tailored infusions of opioids. Mather concludes this subsection with a thought-provoking summary of the basic science section and presents us with some intriguing possibilities for the future.

The clinical section of this volume is also divided into four subsections: (a) routes of administration, (b) oral controlled release morphine, (c) patient-controlled analgesia, and (d) summary on clinical value of systemic opioids. The first subsection, on routes of administration, provides a nice review of both oral and nontraditional routes of administration of opioids including sublingual, transdermal, transnasal, and rectal. The information presented in this section would be of value to any physician who prescribes narcotics.

The second section, on oral controlled release morphine, reviews the results of clinical trials and the clinical pharmacokinetics of this formulation of morphine. Little new clinically useful information is presented. Levy's chapter outlining the clinical use of this drug is concise and presents many useful practical suggestions for the clinician. The third subsection, on patient-controlled analgesia, presents an overview of the subject from the viewpoint of four different authors. Unfortunately, there is a significant amount of duplicate material presented.

The fourth subsection presents two excellent review chapters that are certainly the highpoint of this volume. The first, "Acute Pain: A Review of Its Effects and Therapy with Systemic Opioids" by Benedetti, provides a well-organized review of the physiology and pathogenic effects of acute pain, the effect of opioids on various organ systems, and the subjects of tolerance and adverse effects. The second chapter, "Systemic Opioids for the Management of Cancer Pain," by Bonica and Ekstrom, provides an excellent overview on the problem, etiology, diagnosis, and treatment of cancer pain.

In summary, this book will be of value to the physician or basic scientist who already has a working knowledge of systemic opioids and is interested in obtaining more advanced information on the subject.

Steven D. Waldman, MD
Pain Consortium of Greater Kansas City
Leawood, Kansas

Pediatric Pain. Volume 15 in Advances in Pain Research and Therapy

D. C. Tyler and E. J. Krane, eds. New York: Raven Press, 1990, 404 pp, $95.00.

Pain is a topic with many facets, and pediatric pain may be the most complex of those facets. Evaluation and treatment of pain is difficult enough without the added challenge of dealing with an immature being in whom it is difficult to make objective observations. Fortunately, even those who spend most of their time caring for adults now recognize that pain is experienced by newborns as well as by grown-ups, and are recognizing the need for pediatric pain management.

This volume is a partial report of the First International Symposium on Pediatric Pain, which was held in July 1988. The Symposium transcended disciplinary lines and this volume reflects both the international scope and the multidisciplinary attendance of the meeting. Pain assessment is well-covered, with discussions of the relationship between pain ratings and pharmacologic intervention for children in pain, factors that affect nurses' decisions in medicating children postoperatively, and parent/child agreement in rating the child's pain. Several of the most useful tools for evaluating children's pain are also described. Regional anesthesia for postoperative pain and behavioral management are detailed in other sections, as are chronic nonmalignant and cancer pain.

Probably the most valuable contribution of this well-edited book is that it samples, in one volume, a great number of the researchers in fields other than anesthesiology, with excellent references throughout the compendium. Much of the pioneering work in assessment and nonpharmacologic management of pain in children is being conducted by nurse researchers and psychologists, whose work is unfamiliar to those who do not have a special interest in pediatric pain management. The book would also be a useful reference for departmental libraries, particularly departments in nonpediatric hospitals, where children receive care and where it is only now being recognized that they deserve better pain management. This book, at $95.00, may be useful for anesthesiologists who have an interest in children and who are unfamiliar with the workers from outside anesthesiology. At this price, although the information *should* be of interest to all anesthesiologists, it would not be appropriate for all personal libraries.

Linda Jo Rice, MD
Departments of Anesthesiology and Pediatrics
Children's National Medical Center
The George Washington University School of Medicine
Washington, DC

Spinal Narcotics

Narinder Rawal and Dennis W. Coombs, eds. Boston: Kluwer Press, 1990, 147 pp, $71.95.

Spinal opioids have dramatically changed the practice of anesthesiology. The efficacy and relative safety of this modality has led to its rapid acceptance by patients and anesthesiologists alike. It is not surprising that the use of spinal opioids to control acute and postoperative pain, obstetrical pain, and pain of malignant origin continues to increase. To put this in perspective, consider the fact that, before 1976, essentially no opioids were administered via the spinal route. Yet in 1990, a mere 14 years later, it is estimated that spinal opioids will be used to manage pain in more than 120,000 patients! This rapid transition from basic science animal studies to widespread clinical use has no precedent in the history of anesthesiology.

Dr. Prithvi Raj, series editor, states in his preface that the Current Management of Pain series is intended "to provide up-to-date information on clinical management of acute and chronic pain and related research as quickly as possible," and *Spinal Narcotics*, the fifth volume in the series, provides a concise clinical overview of the rapidly expanding area of spinal narcotics. The fact that Dr. Rawal and Dr. Coombs brought *Spinal Narcotics* from inception to publication in a mere 18 months is reflected in the surprisingly current content of the volume. The editors have avoided the uneveness in readability and repetitiveness so common in the multiauthored edited text.

The detailed overview of opiate receptors and endogenous and exogenous opioids correlates nicely with Gustafson's review of the clinically relevant physiology surrounding the uptake and distribution of spinal opioids. Excellent chapters on the clinical application of spinal opioids and the adverse effects of spinal opioids provide the clinical cornerstone of this volume. Combined with reviews of the role of spinal opioids in obstetrics and implantable delivery systems, this text provides the anesthesiologist with a comprehensive overview of the subject. Future editions of this text might include a chapter on nursing considerations and a "how-to" chapter on implantation techniques and troubleshooting.

In summary, *Spinal Narcotics* will provide the anesthesiologist with a concise, comprehensive, and clinically relevant overview of this rapidly expanding field. The text is readable and well-organized, and represents an excellent addition to the practicing anesthesiologist's library of reference texts.

Steven D. Waldman, MD
Pain Consortium of Greater Kansas City
Leawood, Kansas

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Bonica JJ, Loeser JD, Chapman CR, Fondyce WE, eds. *The Management of Pain*, 2nd ed. Philadelphia: Lea & Febiger, 1990, 2120 pp (two volumes), $225.00.

Brodsky JB, ed. *Thoracic Anesthesia*. Problems in Anesthesia, Volume 4, No. 2. Philadelphia: J.B. Lippincott, 1990, 180 pp, $30.00.

Eltringham R, Durkin M, Andrewes S, Casey W. *Post-anaesthetic Recovery, A Practical Approach*, 2nd ed. New York: Springer-Verlag, 1989, 193 pp, $35.00.

Ferrante FM, Ostheimer GW, Covino BG, eds. *Patient-Controlled Analgesia*. Boston: Blackwell Scientific Publications, 1990, 244 pp, $34.95.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1991 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1991 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **December 14, 1990.** Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1991 Award(s) will be announced at the Annual Scientific Meeting (65th Congress) of the International Anesthesia Research Society to be held at the Marriott Rivercenter, San Antonio, Texas, March 8–12, 1991.

Anesthesiology Review Seminar

Sponsored by Creighton University School of Medicine and Professional Seminars, Inc.

August 12-17, 1990 Hilton Head Island, SC   October 1-6, 1990 Palm Desert, CA

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Attendance at these seminars **will be kept low** to enable faculty and staff to attend to the individual needs of each participant. Only the **first 100** registrations will be accepted.

For a complete list of **topics, faculty or references,** call Professional Seminars, Inc. at 1-800-445-4564 or write to P.O. Box 498, Clinton, IN 47842. To register for either course, call Creighton University, CME Division at 1-800-548-2633.

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ANESTHESIOLOGY

Board Certified/Eligible Anesthesiologist needed as Associate in Section of Anesthesia of 215 member multi-specialty clinic which serves as a referral center for surrounding areas of Northeastern Pennsylvania and the Southern Tier of New York State.

State-of-the-art facility. Medical school teaching affiliation through surgical residency program provides a stimulating environment. Tertiary Care Center performing 10,000 anesthetic procedures per year. Most types of surgery performed with emphasis on cardiovascular and neurosurgery.

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North Shore University Hospital-Cornell University Medical College has immediate openings for qualified applicants. With over 6,000 deliveries per year, our hospital offers a wide variety of obstetrical cases including high risk/tertiary care referrals. Located in Manhasset, NY, a suburb of New York City, North Shore Hospital is a 700+ bed tertiary care center with one of the busiest obstetrical services in the New York metropolitan area.

Interested candidates should send requests to:

Glen Z. Brooks, M.D.
Chief, Division of Obstetrical Anesthesia
North Shore University Hospital
300 Community Drive
Manhasset, NY 11030

For additional information, please contact the Department of Anesthesia at (516) 562-4887.

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WASHINGTON UNIVERSITY MEDICAL CENTER

The expanding Division of Cardiothoracic Anesthesia is currently seeking Board Certified/Board Eligible anesthesiologist to join the faculty. Formal training in cardiac or cardiothoracic anesthesia is required. Responsibilities include administration of anesthesia, teaching of residents and medical students, and participation in research.

Full spectrum of adult cardiac and thoracic surgery, including arrhythmia surgery, active heart and lung transplantation. Excellent opportunities and support for basic and clinical research.

Washington University is an equal opportunity/affirmative action employer. Academic title and compensation will be commensurate with credentials. Address correspondence with references and curriculum vitae to:

Demetrios G. Lappas, M.D.
Washington University School of Medicine
Director, Division of Cardiothoracic Anesthesia
660 South Euclid Campus Box 8054
St. Louis, MO 63110

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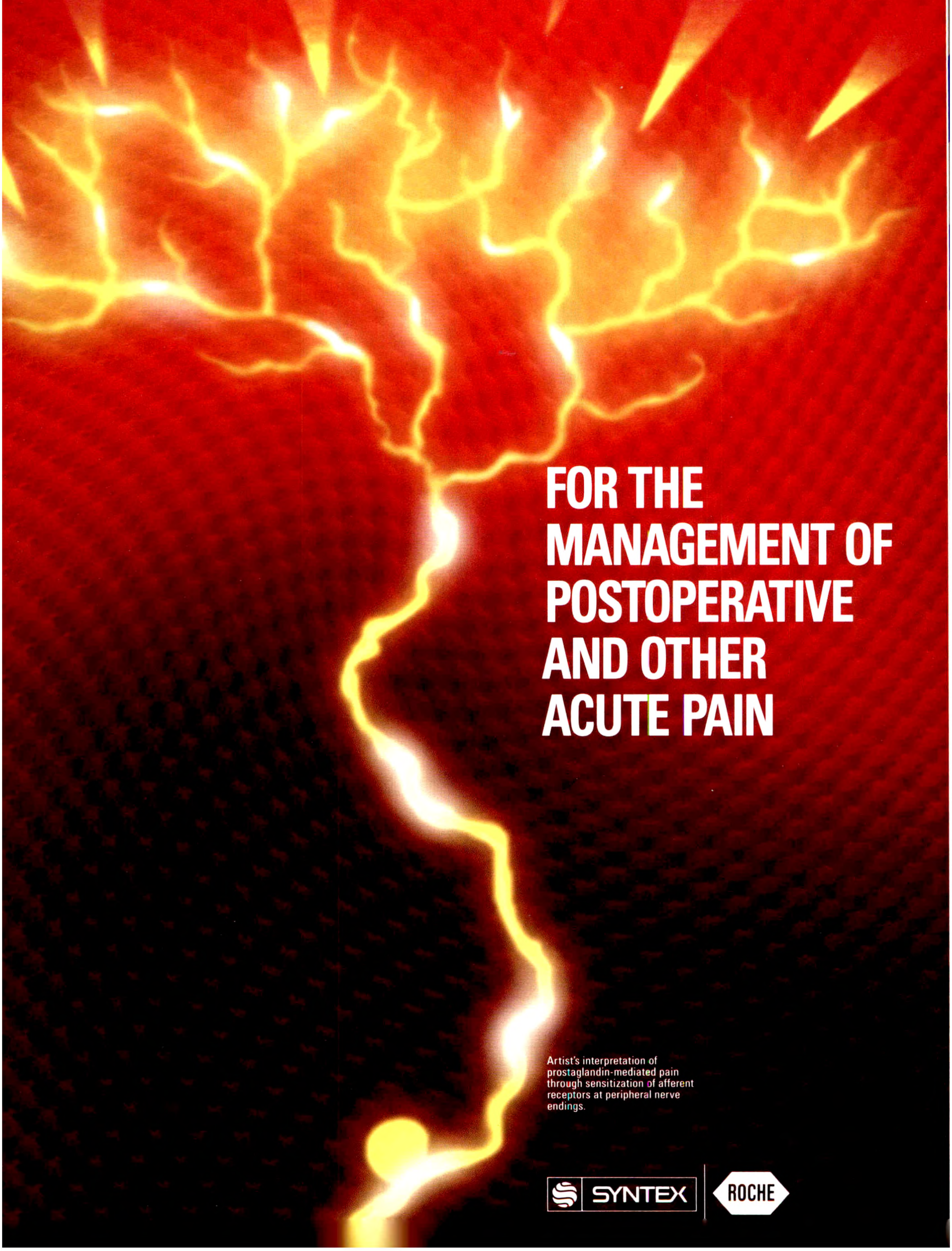
FROM SYNTEX LABORATORIES

THE FIRST INJECTABLE ANALGESIC NSAID



FOR THE MANAGEMENT OF POSTOPERATIVE AND OTHER ACUTE PAIN

Artist's interpretation of prostaglandin-mediated pain through sensitization of afferent receptors at peripheral nerve endings.

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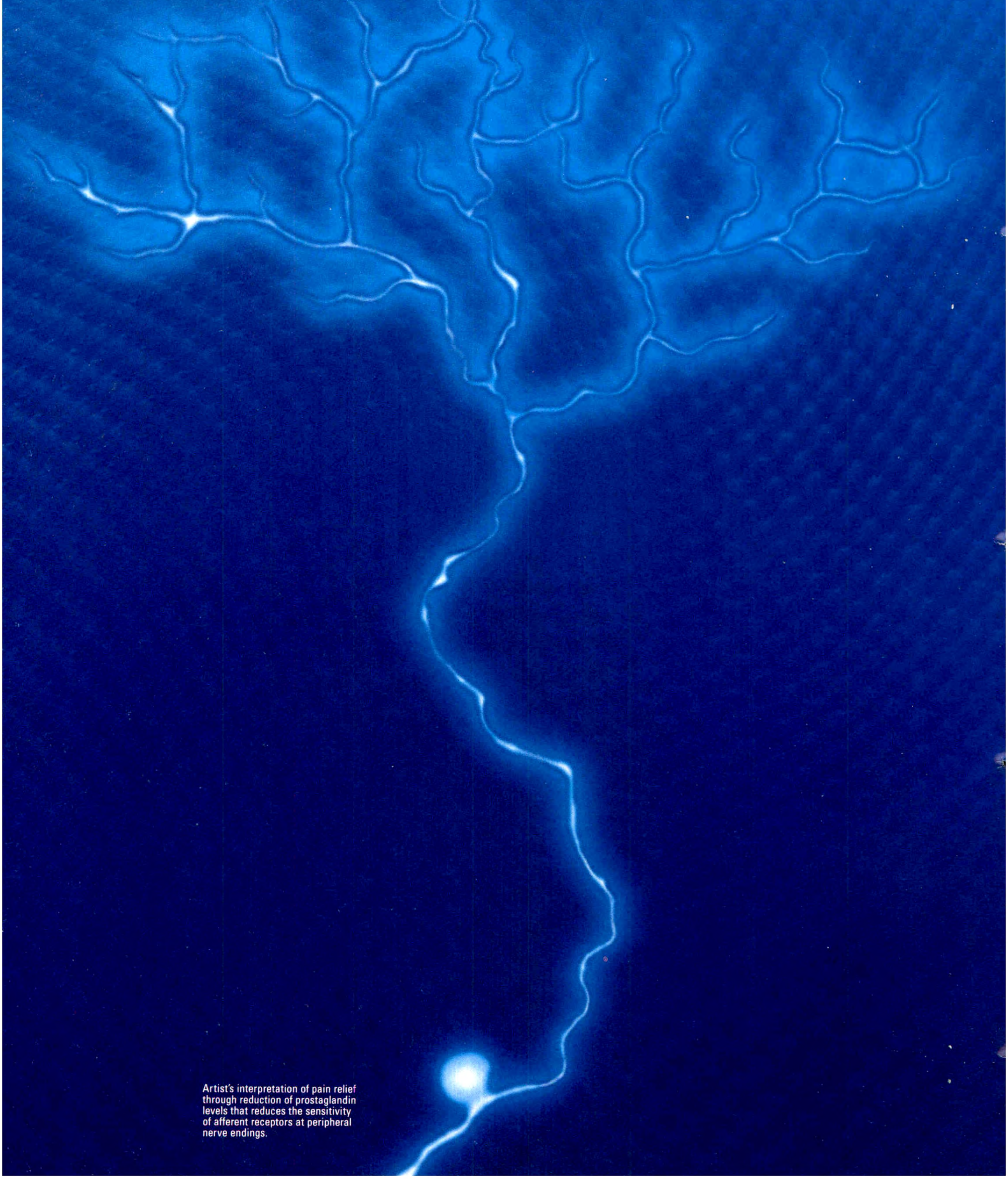


Artist's interpretation of pain relief through reduction of prostaglandin levels that reduces the sensitivity of afferent receptors at peripheral nerve endings.

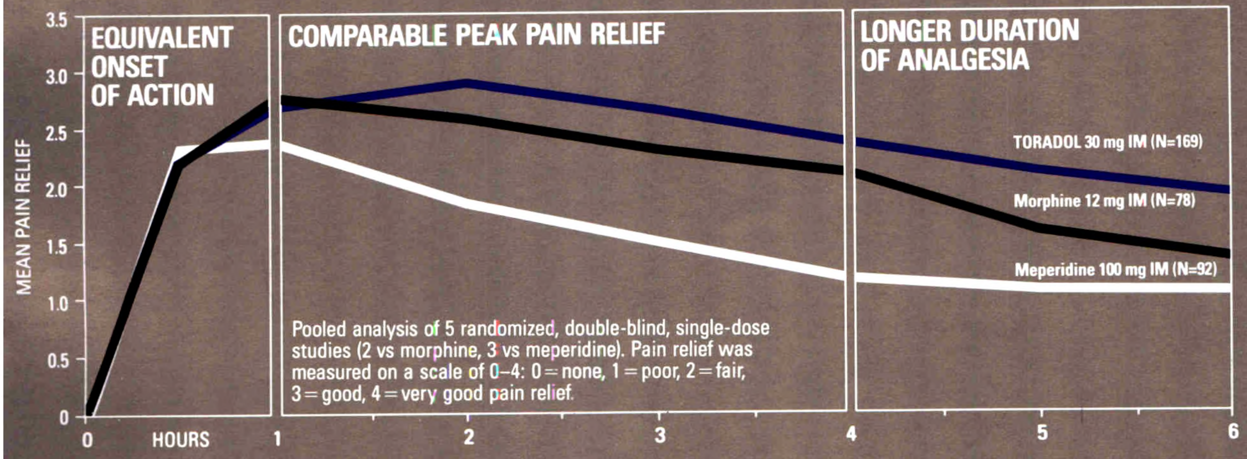
TORADOL® IM INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

The first peripherally acting analgesic with efficacy comparable to morphine 12 mg and meperidine 100 mg

Analgesic efficacy of TORADOL℠ administered 24–72 hours postsurgery[1]



Pooled analysis of 5 randomized, double-blind, single-dose studies (2 vs morphine, 3 vs meperidine). Pain relief was measured on a scale of 0–4: 0 = none, 1 = poor, 2 = fair, 3 = good, 4 = very good pain relief.

Documented efficacy following a broad range of surgical procedures:

General, orthopaedic, gynecologic (not for obstetric use)

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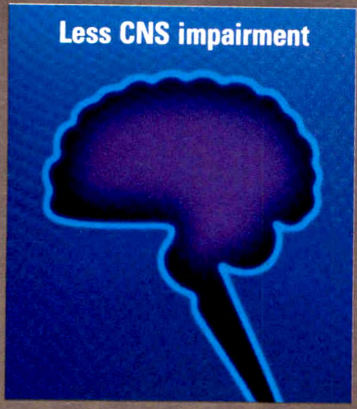
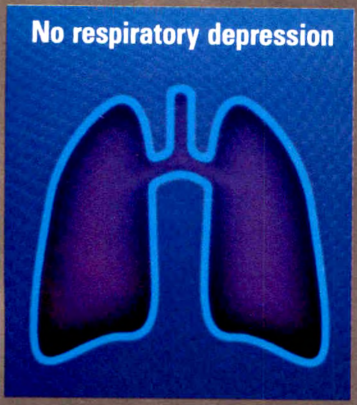
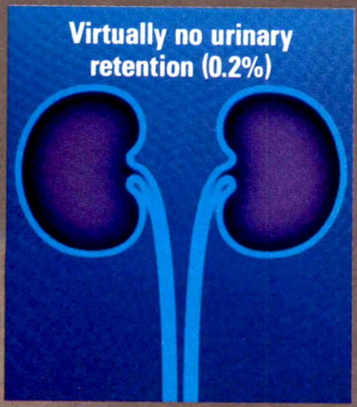
*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings" and "Precautions" sections of prescribing information.

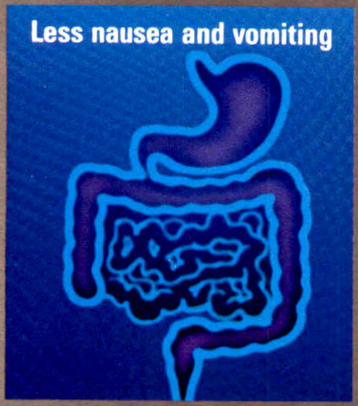
[1] Data on file, Syntex Laboratories, Inc., Document #90037-1.

Please see brief summary of prescribing information on last page of this advertisement.





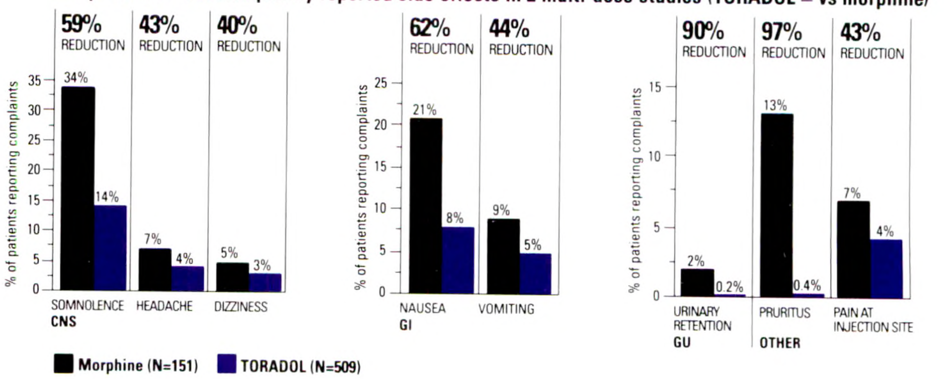




START RECUPERATION WITHOUT NARCOTIC SIDE EFFECTS[1]*

- 62% less nausea and 44% less vomiting
- 48% fewer CNS side effects
- No respiratory depression
- No hypotension
- 1-day earlier resumption of normal bowel function following major abdominal surgery
- No difference in clinically significant postoperative bleeding with TORADOL IM (0.4%) as compared to opiates (0.2%)

Comparison of most frequently reported side effects in 2 multi-dose studies (TORADOL IM vs morphine)**



Adverse reactions rates from short-term use of NSAIDs are generally from 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL IM.

**FOR
POSTOPERATIVE
AND OTHER
ACUTE PAIN**

NEW

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*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings," "Precautions," and "Adverse Reactions" sections of prescribing information.

**Most frequently reported side effects in major body systems with the exception of the cardiovascular system. 2% of patients treated with Toradol reported vasodilation as compared to 1% of patients treated with morphine.

1. Documented in 2 randomized, double-blind, multi-dose studies in which 509 patients received ketorolac 30 mg and 151 patients received morphine 10 mg or morphine 12 mg. Bowel function was evaluated in a subset of 47 patients undergoing gastric bypass surgery. Data on file, Syntex Laboratories, Inc., Document #90037-2.
2. Data on file, Syntex Laboratories, Inc., Document #90037-3.

Please see brief summary of prescribing information on last page of this advertisement.

Analgesic therapy well suited for postoperative use

TORADOL IM is not an opiate

- Does not act on opiate receptor sites
- No potential for abuse
- No special restrictions or controls required

May be an appropriate alternative to narcotics for:

- Patients with narcotic allergy or intolerance
- Patients with a history of, or potential for, drug abuse or dependence

Special advantages may facilitate postoperative recuperation

- Patients with COPD or the obese–no negative effects on pulmonary function
- Ambulatory surgery patients–less CNS impairment (e.g., 59% less somnolence and 40% less dizziness)

Optimize analgesia on the day of surgery

- On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing
- On average, only one supplemental dose of narcotics may be required[2]

TORADOL® IM
INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

FOR
POSTOPERATIVE
AND OTHER
ACUTE PAIN

NEW TORADOL® IM INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

OPTIMIZE ANALGESIC THERAPY FOR THE POSTOPERATIVE PATIENT

PROPER DOSAGE POSTOPERATIVELY

For maximum analgesia:

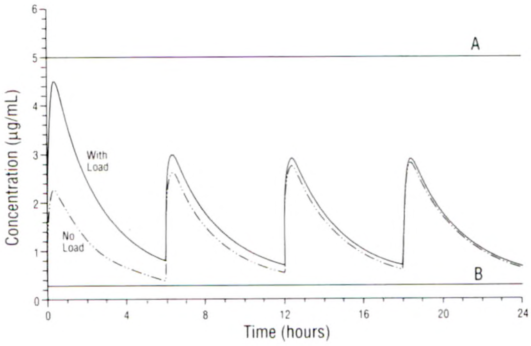
- Give patients prompt pain relief: start with loading dose of 60 mg IM
- Follow with maintenance dose of 30 mg IM Q6h to control pain
- The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter*

Simulated incremental plasma concentrations after 2 multi-dose regimens: (1) TORADOL$^{\text{IM}}$ 30 mg Q6h (no load); (2) TORADOL$^{\text{IM}}$ 60 mg LOADING DOSE followed by 30 mg Q6h

A = Plasma concentration above which side effects are more frequent

B = Estimated concentration required to obtain 50% decreases in pain intensity scores in dental surgery pain

Achieve optimal peak and trough plasma levels by starting with a loading dose (e.g., 60 mg), while maintaining plasma levels within the recommended therapeutic range. Follow with maintenance doses (e.g., 30 mg every 6 hours) to keep plasma levels in the optimal range.



Patient Selection: Use in patients with moderate-to-severe postoperative pain following general, orthopaedic, or gynecologic surgery (not for obstetric use)

Lower doses:

- Recommended for patients under 50 kg (110 pounds), patients over 65 years of age, and patients with reduced renal function
- Start with loading dose of 30 mg IM
- Follow with maintenance dose of 15 mg IM Q6h to control pain

On the day of surgery, some TORADOL$^{\text{IM}}$ patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing (not compatible in same syringe)

*Dosages above those recommended are not associated with commensurate increases in efficacy.

Please see brief summary of prescribing information on last page of this advertisement.

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New! Presenting today's best diagnostic methods and treatment options in pulmonary medicine

Concise Textbook of Pulmonary Medicine

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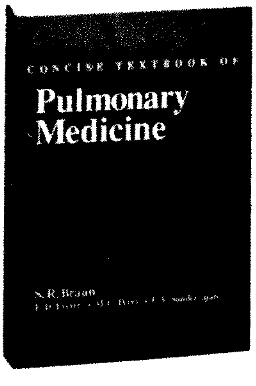

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TORADOL* IM (ketorolac tromethamine)

Brief Summary
TORADOL is a nonsteroidal anti-inflammatory drug (NSAID) TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP and 6 68 mg sodium chloride in sterile water The 30 mg/mL solution contains 10% (w/v) alcohol, USP and 4 35 mg sodium chloride in sterile water The pH is adjusted with sodium hydroxide or hydrochloric acid **Indications and Usage:** Indicated for the short-term management of pain Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation Not recommended for routine use with other NSAIDs because of the potential for additive side effects TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam Studies with other NSAIDs have not been done Has been used concomitantly with morphine and meperidine without adverse interactions **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs **Warnings:** Although TORADOL Injection is recommended for short-term use only, long term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc , no risk factors (e g , age, sex) have been associated with increased risk Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population High doses of an NSAID probably carry a greater risk of these reactions In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity **Precautions:** Impaired Renal or Hepatic Function As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease Renal Effects As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow In these patients, an NSAID may precipitate overt renal failure Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly Discontinuation of the NSAID is typically followed by recovery Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions Hepatic Effects With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients These may progress, remain unchanged, or disappear with continued therapy Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction Hematologic Effects TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT) Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 μg/mL) TORADOL does not alter digoxin protein binding At therapeutic concentrations of salicylate (300 μg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels, hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected In another study of 12 healthy volunteers, co-administration of heparin 5000 U s c and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration This has not been studied with TORADOL Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity This has not been studied with TORADOL TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity Ketorolac was not mutagenic in tests with S typhimurium, S cerevisiae, or E coli and did not cause chromosome breakage in the in vivo mouse micronucleus assay Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs There are no adequate and well-controlled studies in pregnant women TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037 After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman **Pediatric Use:** TORADOL is not recommended for use in children **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage This is also true for TORADOL In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days **Incidence greater than 1%:** Body as a whole edema GI nausea,* dyspepsia,* GI pain,* diarrhea Nervous system drowsiness,* dizziness, headache, sweating Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine) *Incidence of reported reaction 3%-9%. Reactions occurring in less than 3% are unmarked **Incidence 1% or less:** Body as a whole asthenia, myalgia Cardiovascular vasodilation, pallor Dermatologic pruritus, urticaria GI constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting Hemic and lymphatic purpura Nervous system dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory dyspnea, asthma. Special senses abnormal taste, abnormal vision Urogenital increased urinary frequency, oliguria **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing Patients receiving TORADOL orally for ≥6 months have not developed tolerance and there is no pharmacologic basis to expect addiction TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action In vitro, TORADOL does not bind to opiate receptors Thus, TORADOL does not have central opiate-like activity **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses >100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function CAUTION Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others

Mfd for Syntex Laboratories, Inc
Palo Alto, CA 94304
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SYNTEX

02-2434-40-00 December 1989

EEG AND EVOKED POTENTIALS: INTRAOPERATIVE AND ICU MONITORING

January 3-6, 1991
The Buena Vista Palace
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Course Directors: Betty L. Grundy, M.D., Michael E. Mahla, M.D. and William A. Friedman, M.D.

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A distinguished faculty will present indications methods, and interpretation techniques for EEG and evoked potential monitoring. Participants will be divided into small groups for a more personal, hands-on approach, using a wide variety of EEG and evoked potential systems.

Course tuition is $500 ($550 after November 30, 1990). Cancellation of registration by written notification only prior to December 1, 1990. There is a $50 cancellation fee. This program will be approved for Category 1 credit toward the Physicians Recognition Award of the American Medical Association.

For complete information contact Mrs. Carolyn Schoenau, Program Coordinator, Anesthesiology Alumni Association of Florida, Inc., Post Office Box 13417, Gainesville, Florida 32604 (Area code 904 392-8959).

State University of New York at Buffalo Seeks Anesthesiology Chairman

The State University of New York School of Medicine at Buffalo is seeking a Chairman to direct the teaching, research, and patient care missions of its Department of Anesthesiology. Qualifications include an M.D. Degree, board certification in Anesthesiology, record of academic and clinical excellence, national recognition as an investigator and commitment to undergraduate and graduate medical education. The composition of the University program offers unusual opportunity for development including multiple academic teaching hospitals, one of which is an outstanding pediatric facility and the other, an internationally recognized regional cancer referral center. Other unusual features of the program including an active cardiac surgery program including one of the two regional cardiac transplant centers in the state of New York, major level I trauma center including the only pediatric trauma center in the state of New York, a free standing pediatric obstetric center and an active multidisciplinary neurosurgical program. Because of the multiple sites composing this University's environment, substantial previous experience in administration within an academic setting would be ideal.

This position would include tenured faculty appointment and the University at New York is an Affirmative Action/Equal Opportunity Employer. Respond to:

Lawrence Jacobs, M.D.
Chairman, Anesthesiology Search Committee
Buffalo General Hospital
100 High Street
Buffalo, New York 14203

Anesthesia
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This 200 physician, multi-specialty group seeks Board Eligible/Board Certified physicians desiring 1990 or 1991 practice opportunities. The group is hospital-based in Northeastern Pennsylvania at the New York border. Our state-of-the-art facility offers medical school teaching affiliations as well as clinical research opportunities. Residency programs are conducted in Internal Medicine and General Surgery. Physicians seeking challenging and rewarding practice opportunities, excellent salaries and benefits, combined with rural living and endless recreational opportunities are encouraged to submit a letter and curriculum vitae to:

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Medical Director

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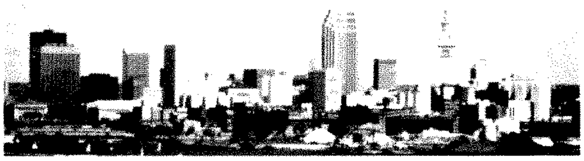

Kaiser Permanente offers the career stability and support of the largest and most experienced pre-paid group medical practice in America. Our physicians begin with an immediate patient base in their specialty. We take care of all the business aspects. You do what you do best — deliver exceptional patient care. We currently have opportunities for board certified/eligible physicians in

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THEN THERE IS OUR IDEAL LOCATION. When you join us in northeastern Ohio you'll enjoy a thriving metropolitan setting... an excellent housing climate... acclaimed symphony orchestra... and a growing group practice with more than 205,000 members in the Cleveland-Akron area.

If you share our perspective, contact us. We offer relocation and spousal assistance programs... attractive salary... full malpractice coverage... company-paid retirement plan... Please send your resume to: **Ronald G. Potts, M.D., Medical Director, Ohio Permanente Medical Group, Inc., Dept. HRAA, 1300 E. 9th Street, Suite 1100, Cleveland, OH 44114. Or call us at 1-800-837-OPMG.** EOE.

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Classified Advertising

ANESTHESIOLOGIST
Full-time anesthesiologist, BC or BE to fill available position immediately. Excellent salary, pension plan, malpractice, health, life, and disability insurance. Diverse caseload. Send CV and three references to Box 411.

411E/H

NEW HAMPSHIRE
Opening for board-certified anesthesiologist to join four MDs and six CRNAs in 190-bed modern community hospital. All types of surgery except cardiac. Moderate obstetrics. Must be energetic and good with epidurals and invasive lines. Excellent fringe benefits and early partnership. One hour drive to seacoast, ski resorts, and Boston. Send CV to Prospect Anesthesia Services, P.C., 10 Prospect Street, Nashua, NH 03060.

419E/J

ANESTHESIOLOGY RESIDENCY POSITIONS
Electronic Bulletin Board listing available. Residency positions for CA-1 through CA-3 and fellowship years in anesthesiology. Use telecommunication software on a computer (300 or 1200 baud, 8 data bits, 1 stop bit, no parity) to call (716) 473-4246, answer "yes" to the first question, and then follow the menus. This is a service provided by the Association of Anesthesiology Program Directors and the Department of Anesthesiology at the University of Rochester, Rochester, New York.

424F/L

ANESTHESIOLOGIST
Board certified/board eligible, to join a four-member incorporated group with CRNAs, 420-bed community hospital with 7000 cases per year in western Pennsylvania, close to large metropolitan areas. Excellent schools, recreational facilities, friendly community. All types of anesthesia with minimal OB. Reply to Box 428. Fellowship or experience in cardiac anesthesia preferred.

428F/I

UNIVERSITY OF ARIZONA
Expanding University program creates exciting opportunities for new faculty, both academic (tenure) and clinical tracks. Applicants must be interested in academic career. Interested particularly in cardiac, obstetric, ICU, and pediatric subspecialties. An AA/EOE. Contact Burnell R. Brown, Jr., MD, PhD, Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ 85724. Closing date: 12/31/90 or until position is filled.

434F/I

OHIO STATE UNIVERSITY, COLUMBUS
The Department of Anesthesiology is recruiting board certified/eligible anesthesiologists for clinical/tenure track appointments at the Instructor, Assistant, Associate, and Professor levels. Responsibilities will include resident and medical student teaching, independent research, and patient care. We are an Affirmative Action/Equal Opportunity Employer. Please send CV to J.S. McDonald, MD, Professor and Chairman, Ohio State University Hospitals, Department of Anesthesiology, 410 West 10th Avenue, Columbus, OH 43210.

435F/H

TENNESSEE
Anesthesiologist: Periodically full-time positions become available at the level of Instructor/Assistant Professor. Applicants must be board certified or in the board process and be interested in resident teaching and clinical research. Tennessee license required. If you would be interested in having your name on file, please reply with curriculum vitae to John T. Chesney, MD, Interim Chairman, Department of Anesthesiology, University of Tennessee Medical Center at Knoxville, 1924 Alcoa Highway, Knoxville, TN 37920. UTMC is an Affirmative Action/Title IX/Section 504 Employer.

436F/L

NEW YORK
CA 3 or 4 fellowship positions at Memorial Sloan-Kettering Cancer Center beginning July 1991. Straight clinical and clinician-investigator opportunities available in critical care medicine, pain management, and anesthesia for thoracic and neurological surgery. Send CV and summary of career goals to Robert F. Bedford, MD, Chairman, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

393F/H

ANESTHESIOLOGIST
BE/BC needed to join three-man group in Midwest. Send inquiries, CV, and references to Box 442 G/I.

442G/I

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA, SAN DIEGO is recruiting for four faculty positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol driven human studies. The three other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anes-

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum 1/4 page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212)685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.10 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $15.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia* Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

thesia. One of the four positions may be tenured track. Otherwise the positions are nontenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in Anesthesiology and a California Medical License is required. Possession of a certificate of special qualifications in Critical Care Medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego, is an Equal Opportunity/AA Employer. All applications received by October 31, 1990 will receive thorough consideration.

445G/I

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity/affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

446G/L

ANESTHESIOLOGIST
Two BE/BC to join rapidly growing practice in Mobile, Alabama. Early partnership, competitive starting salary. Qualified applicants please send CV to Michael P. Ederer, DO, 3401 Medical Park Drive, Suite 107, Mobile, AL 36693.

447G/I

OREGON
Obstetric Anesthesia: Adding second faculty member at assistant professor level with emphasis on obstetric anesthesia and related research. Will participate in regular OR duties. Experience or training in OB anesthesia required. Required ABA or equivalent certification or must be in ABA exam system. Must be eligible for Oregon license. Send CV and names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

450G/I

BE/BC ANESTHESIOLOGIST
Southwest Pennsylvania, 300-bed, modern community hospital to work with three MDs and CRNAs. Competative starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to Box 454G/I.

454G/I

WISCONSIN
Milwaukee, on Lake Michigan, America's "most livable city" with extensive cultural and recreational opportunities. Opening for clinical BC/BE anesthesiologist at the Medical College of Wisconsin Section of Obstetric Anesthesia. Obstetric Anesthesia fellowship or extensive experience necessary. Position involves at least 50% time spent teaching residents at a large community hospital with level III nursery and > 45% patients with anesthesia department intervention. Patient population is mix of 85% private/15% clinic patients. Other clinical or research time may be spent in Department of Anesthesiology, a 50+ member department that trains residents, fellows, and has an extensive laboratory available. Salary and academic position commensurate with experience. MCW is an equal opportunity employer. Reply with CV to Anita Maitra-D'Cruze, MD, Director of OB Anesthesiology, St. Joseph's Hospital, 5000 West Chambers Street, Milwaukee, WI 53210.

455G/I

OHIO STATE UNIVERSITY, COLUMBUS
The Department of Anesthesiology is recruiting board certified/eligible anesthesiologists as a Director of Ambulatory Surgery with specific training and/or experience in adult outpatient surgery. Responsibilities include management of 40–50 patients per day case load as well as resident teaching, research, and patient care. We are an Affirmative Action/Equal Opportunity Employer. Please send CV to Chairman, Faculty Search Committee Ohio State University Hospitals, Department of Anesthesiology, 410 West 10th Avenue, Columbus, OH 43210.

457G/J

NURSE ANESTHETIST
The Carl Vinson V. A. Medical Center, located in the pleasant, sunny community of Dublin, Georgia within easy driving distance to most major cities of Georgia, recreational parks, etc., is currently recruiting for a nurse anesthetist. Hours are 7:30 AM until 4:00 PM, Monday–Friday, and rotate on-call duty. Generous salary plus benefits including 5 weeks paid vacation and 13 days earned sick leave per year, health plan, life insurance, federal retirement system, and continuing education seminars. For further information, contact K. R. Varma, MD, Acting Chief of Surgery, (912) 272-1210, Ext. 215 or 217, or E. Gordon King, MD, Chief of Staff, (912) 272-1210, Ext. 202.

458H

CRNAs
North Central Florida anesthesia group is seeking experienced certified registered nurse anesthetists. 250-bed HCA hospital—no weekends, OB, trauma, or open heart cases. Reply to Box 459H.

459H

COME TO THE NATION'S CAPITAL
Associated Anesthesiologists Service, P.C. (AAS) is seeking qualified physicians to join its practice. AAS is a private practice anesthesia group providing services to the Washington Hospital Center (WHC), an 871 tertiary care facility in the heart of the District. We perform approximately 17,000 surgical procedures annually including 150 kidney transplants. Washington Heart, a renowned program affiliated with WHC performs 1600 open heart procedures yearly including transplant. New facilities, opened in November 1989, include an 18-room operating suite with laser capability, holding and induction areas, and neurosurgical unit.

Physicians completing their training are welcome. All applicants must be board eligible or board certified and possess or be able to obtain a license to practice in the District of Columbia.

For information, please call Mary Ann Coffey at (301) 589-0931 or FAX or mail your CV to Associated Anesthesiologists Service, P.C., 818 Roeder Road, Suite 409, Silver Spring, MD 20910. FAX (301) 587-9276.

460HI

ANESTHESIOLOGIST
BC/BE to join group of 10 MDs with CRNAs in a large hospital located in a pleasant midwestern community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and OB. Excellent starting salary and benefits package leading to early partnership. Send CV to Associated Anesthesiologists of Toledo, Inc., 2409 Cherry Street, Suite 4, Toledo, OH 43608.

461H/J

SUBURBAN MIDWEST
Anesthesiologists, BE/BC, needed to assist in open heart surgery and other areas. Attractive salary with excellent fringe benefit program. Send curriculum vitae to Michael Stelmacki, 1 Insurance Center, Suite 101, Creve Coeur, MO 63141.

462H

ANESTHESIOLOGIST
BC/BE to join small group at a modern community hospital in south central Pennsylvania. All types of anesthesia, including open heart. Close to metropolitan areas,

good school systems, recreational facilities; excellent benefits, early partnership. Please send CV. Reply to Box 463H/J.

463H/J

CARDIAC ANESTHESIA FELLOWSHIP

Wake Forest University Medical Center offers a 12-month research fellowship in cardiac anesthesia. Both clinical and animal research opportunities are available. The program is designed for candidates completing a 4-year anesthesiology residency continuum who desire academic careers in cardiothoracic anesthesia. Six months or more of cardiac anesthesia at the CA-3 level is a prerequisite. Individuals who have completed anesthesia training programs in other countries are also encouraged to apply. For further information, please write Glenn P. Gravlee, MD, Head, Section on Cardiothoracic Anesthesia, Wake Forest University Medical Center, 300 South Hawthorne Road, Winston-Salem, NC 27103, AA/EOE.

464H/J

ANESTHESIOLOGIST

BC/BE needed in group practice of eight in Cleveland area. Send resume to J.S. Anesthesia & Associates, 4229 Pearl Road, Cleveland, OH 44109. (216) 351-3440.

465H

CALIFORNIA

Anesthesiologist needed for Palm Springs group practice. Resort community. All types of anesthesia except heart and trauma. Excellent compensation package leading to partnership. Please send CV to Director of Anesthesia, 81880 Dr. Carreon Drive, B207, Indio, CA 92201.

466H

VERMONT

Second anesthesiologist for growing department in modern, 80-bed, acute care hospital. Fee-for-service practice. Lakeside community close to excellent skiing. Income guarantee. Moving expenses. Send CV to New England Health Search, 63 Forest Avenue, Orono, ME 04473. (207) 866-5680 or (207) 866-5685.

467H/J

LOUISIANA

Anesthesiologist. Board-certified or -eligible anesthesiologist to fill clinical faculty positions at a University Medical Center. The position responsibilities include administration of anesthesia, teaching of residents, and supervision of CRNAs. Encouragement will be given to initiate or participate in research. Faculty rank and salary will be commensurate with experience. Louisiana State University Medical Center, School of Medicine in Shreveport is an affirmative action/equal opportunity employer. Send curriculum vitae to D. Richard Davis II, MD, Chairman, Department of Anesthesiology, LSU Medical Center, P.O. Box 33932, Shreveport, LA 71130-3932.

468H/A

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY

The Department of Anesthesiology of the Medical College of Wisconsin is accepting applications for a 12-month fellowship in pediatric anesthesiology beginning January 1, 1991 (all candidates should have completed the CA-3 year). Experience and training will include all aspects of pediatric anesthesiology including cardiac anesthesia and pain management. Opportunity also is provided for clinical research and critical care experience. Inquiries, CV, and references should be sent to Stephen P. Pontus, MD, Section of Pediatric Anesthesiology, Children's Hospital of Wisconsin, P.O. Box 1997, M.S. 735, Milwaukee, WI 53201.

469H/J

SARANAC/LAKE PLACID, NEW YORK

Third anesthesiologist to join well-established, fee-for-service group affiliated with 90-bed, acute care hospital. Four-season recreation area in beautiful Adirondack region. Send CV to New England Health Search, 63 Forest Avenue, Orono, ME 04473 or call (207) 866-5680 or (207) 866-5685.

470H/J

TENNESSEE—ANESTHESIOLOGY

Full-time positions at levels of Instructor to Associate Professor with emphasis on teaching, patient care, and clinical research. Prerequisites are (1) meet Tennessee license requirements and (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send CV, bibliography, and the names of three references to John Zanella, Jr, PhD, MD, Vice Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163.

The University of Tennessee, Memphis is an Equal Employment Opportunity/Title IX Section 504/Affirmative Action Employer.

471H/J

PACIFIC NORTHWEST

Position available for board certified or soon to be board certified anesthesiologist. Send CV and date available to Box 472H/A.

472H/A

PEDIATRIC ANESTHESIOLOGIST

The Alfred I. duPont Institute Children's Hospital of the Nemours Foundation is recruiting a pediatric anesthesiologist to join a rapidly developing pediatric anesthesia practice in a privately endowed children's hospital. We are seeking a board-certified anesthesiologist who desires a position that allows participation in research, administrative responsibilities, and direct patient care.

The Alfred I. duPont Institute is an expanding, 100-bed children's hospital located on a 300-acre estate just northwest of Wilmington, Delaware and 30 minutes south of Philadelphia. For more information, please send your curriculum vitae to Robert G. Kettrick, MD, Director, Departments of Anesthesiology and Critical Care, Alfred I. duPont Institute, P.O. Box 269, 1600 Rockland Road, Wilmington, DE 19899.

474H

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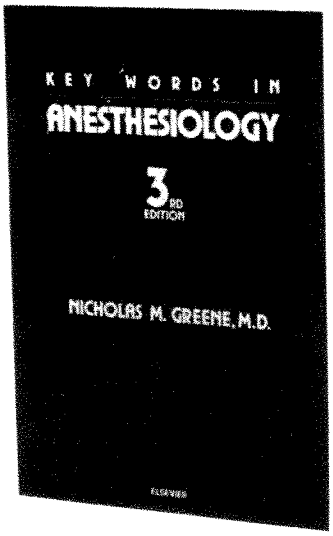

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In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

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▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3 4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

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See following page for brief summary of prescribing information.

Norcuron®

(vecuronium bromide) for injection

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THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.
WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.
PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.
Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.
Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.
Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.
Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.
Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.
Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.
C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.
Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.
Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.
Drug/laboratory test interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.
Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.
Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.
ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.
OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.
DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.
Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug µg/kg/min	Patient Weight – kg 40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.
COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
STORAGE: 15-30°C (59-86°F). Protect from light.
AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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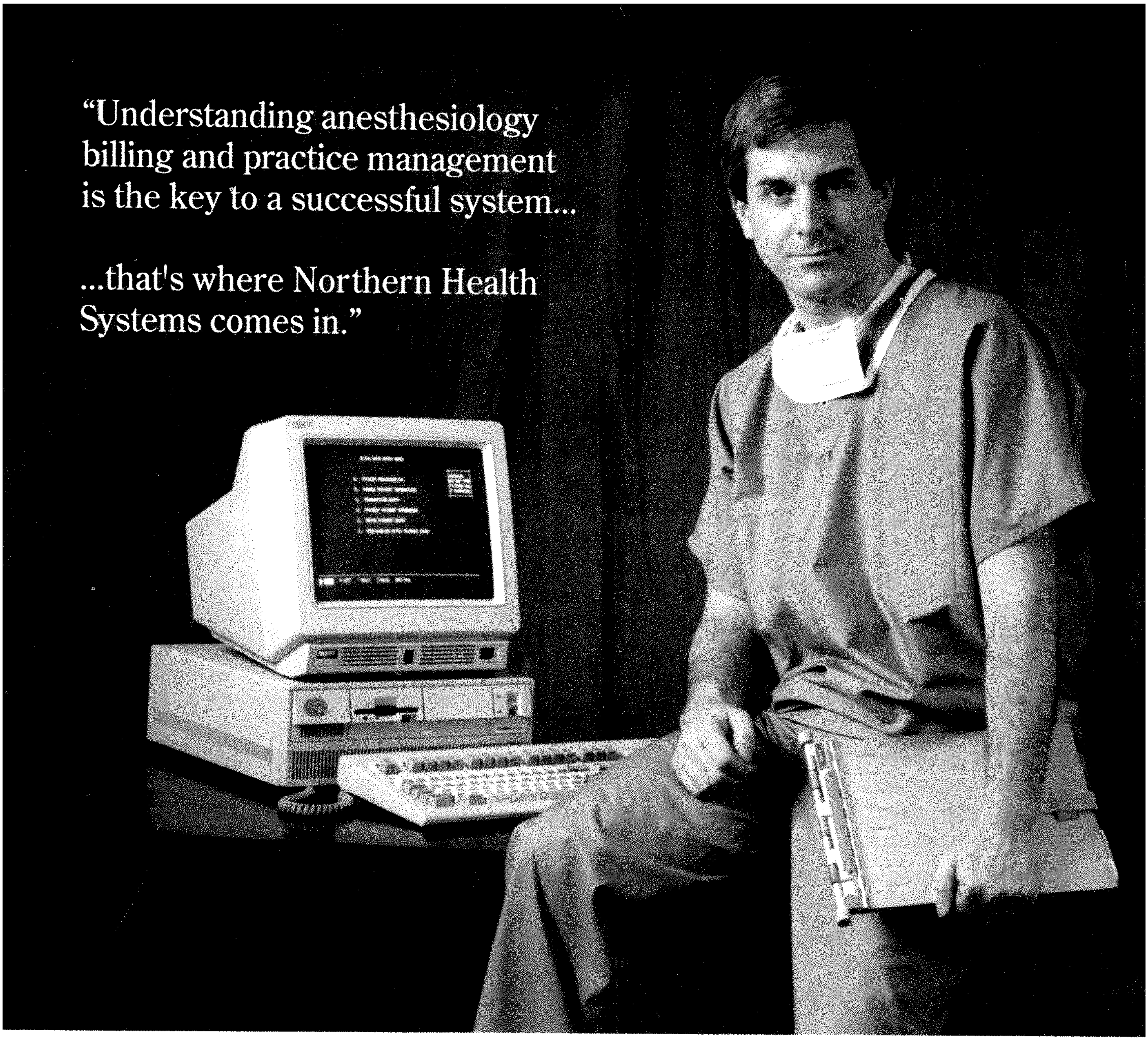
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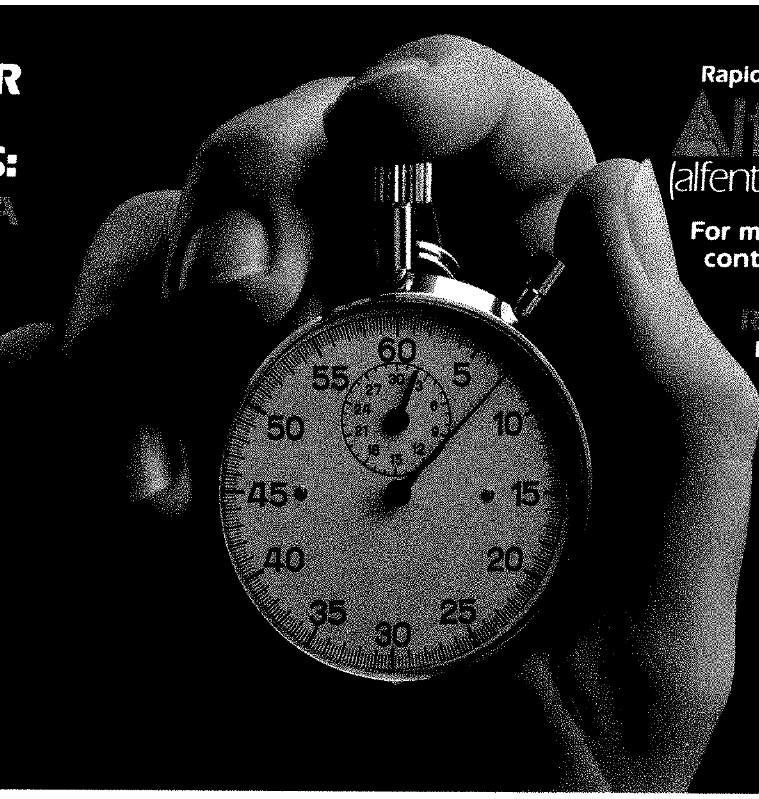

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SHORT DURATION

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Postoperative respiratory depression is of short duration*

***As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.**

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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Anesthesia and Analgesia

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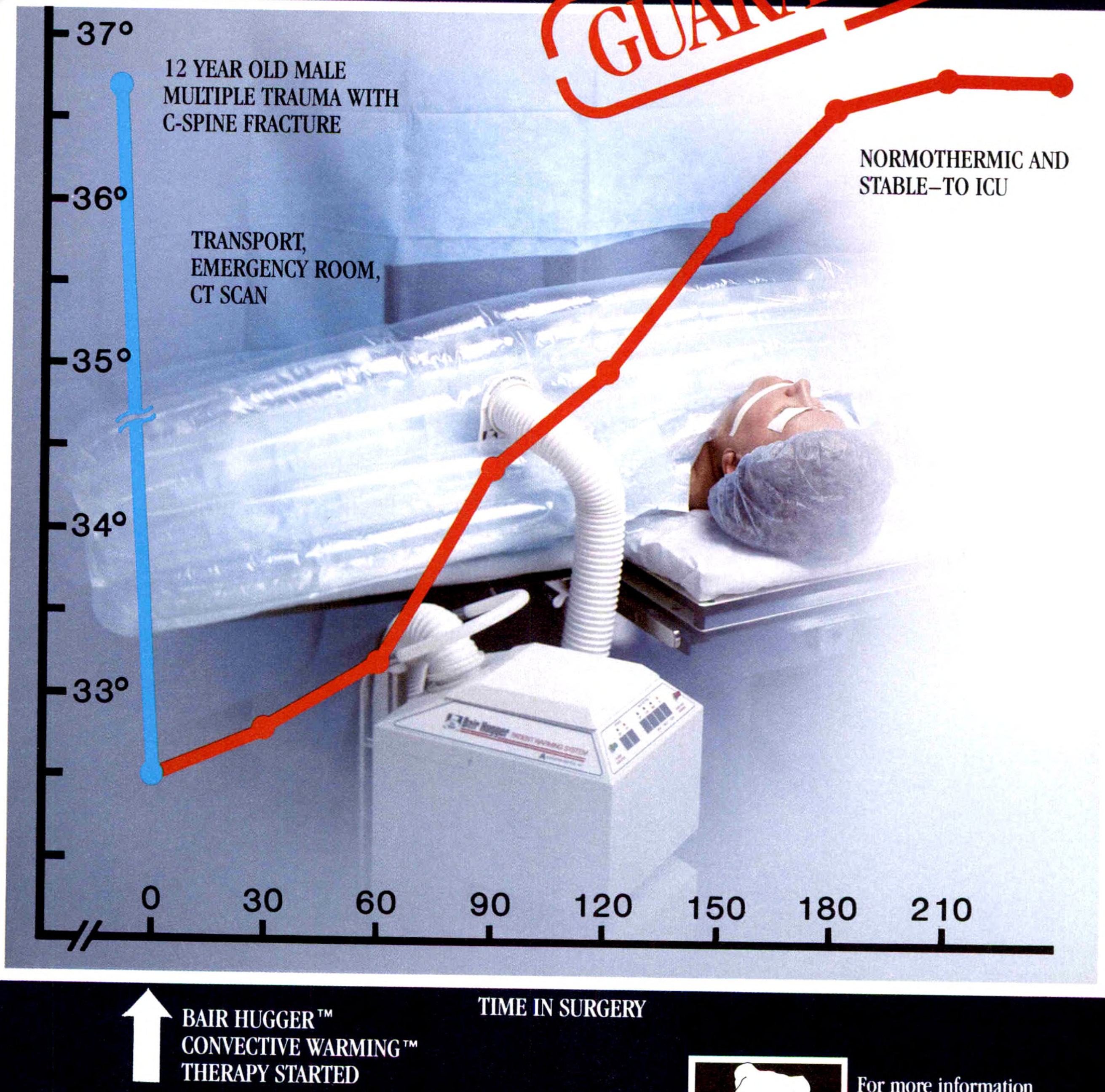

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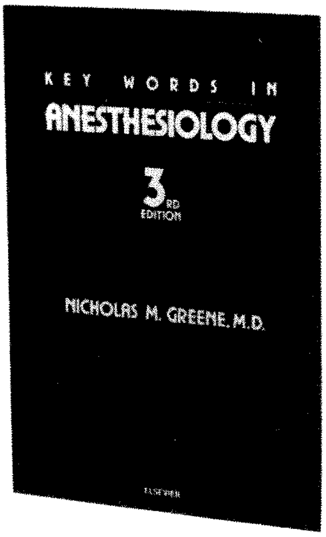

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INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

1. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. *Anesthesiology.* 1984;61:444-453.
2. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172.
3. Lawson DH, Paice GM, Glavin RJ, et al. Atracurium — a post-marketing surveillance study: U.K. study and discussion. *Br J Anaesth.* 1989;62:596-600.

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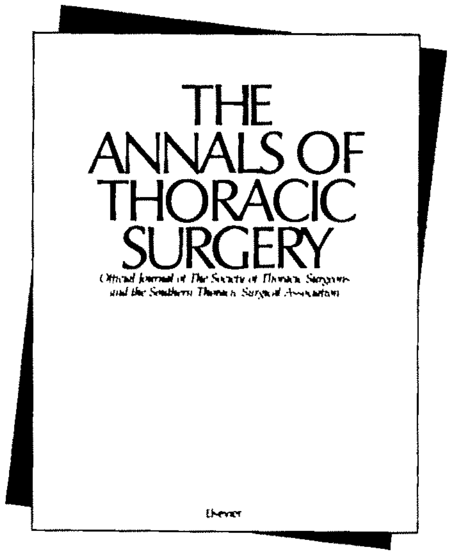

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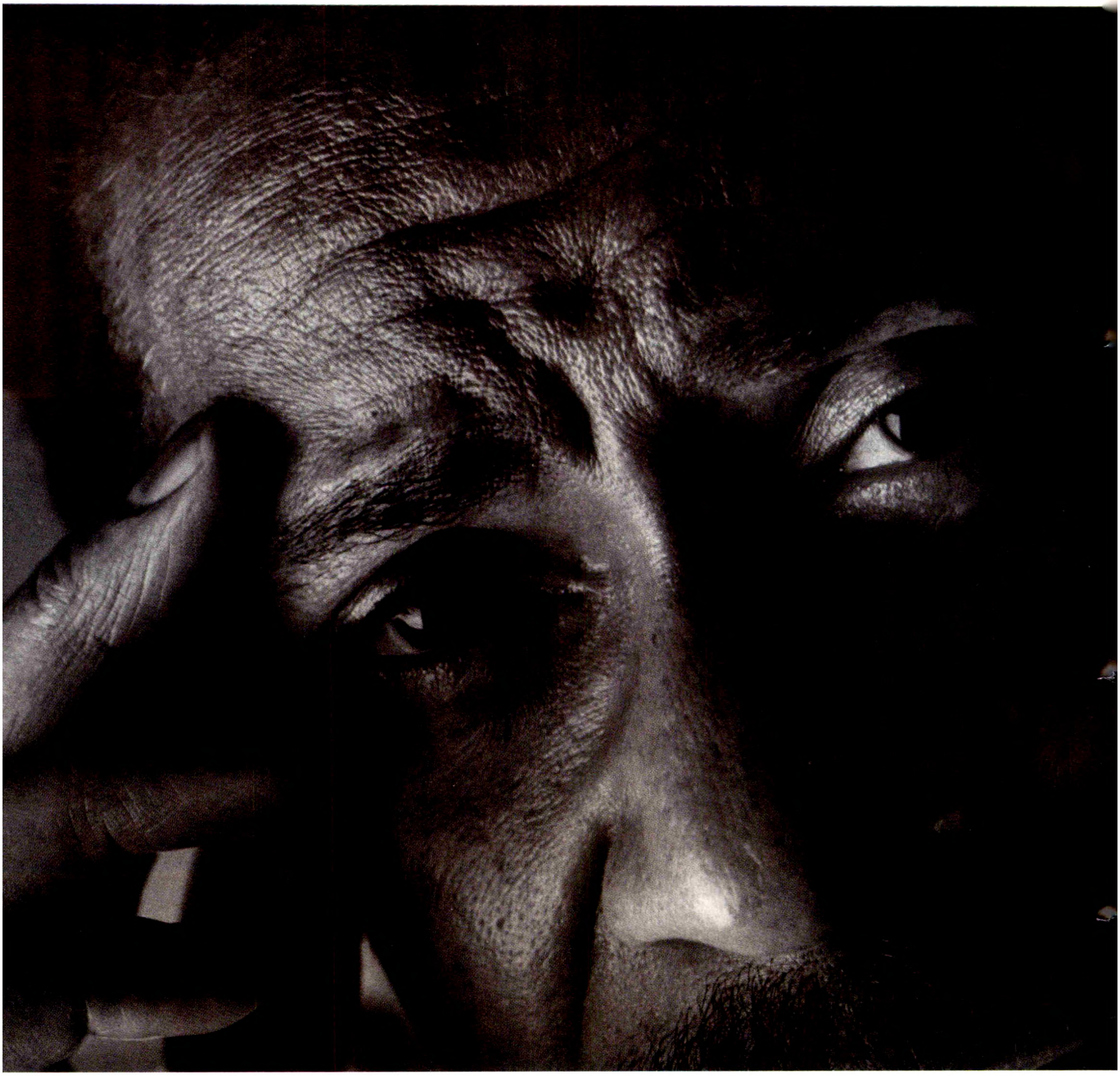

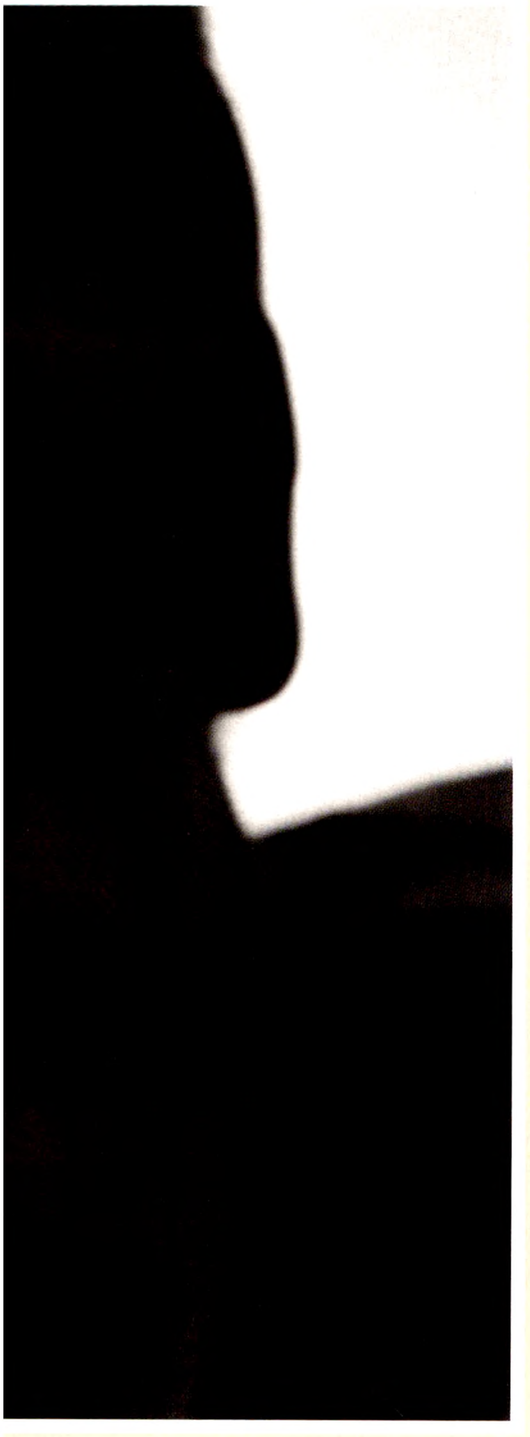

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Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

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Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count, hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/mL (normal 0.0–7.0 mg/mL) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS

The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing) bleeding due to hemodilution (see Warnings), and circulatory overload and pulmonary edema (see Precautions).

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion: HESPAN is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred.

Dosage in Leukapheresis

250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The safety and compatibility of other additives have not been established.

HOW SUPPLIED

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

HESPAN is supplied sterile and nonpyrogenic in 500 mL intravenous plastic infusion containers (NDC 0056-0037-44) and 500 mL intravenous glass bottles (NDC 0056-0037-05).

CAUTION

Federal (USA) law prohibits dispensing without prescription.

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Age-Related Cognitive Recovery After General Anesthesia

F. Chung, MD, C. Seyone, MD, B. Dyck, MD, A. Chung, MD, D. Ong, MD, A. Taylor, PhD, and R. Stone, MD

CHUNG F, SEYONE C, DYCK B, CHUNG A, ONG D, TAYLOR A, STONE R. Age-related cognitive recovery after general anesthesia. Anesth Analg 1990;71:217–24.

This study was designed to quantify the rate of mental recovery in elderly and young patients after general anesthesia for intraabdominal surgery (cholecystectomy). Forty patients (25–83 yr) were given four tests assessing neuropsychological function once preoperatively and on five occasions postoperatively. Two of the four neuropsychological tests showed impairment in scores in the elderly patients on the first postoperative day (Symbol Digit Modalities Test, $P < 0.004$; The Trail Making Test, $P < 0.03$). In addition, one of the tests (Symbol Digit Modalities Test) showed a deterioration in the younger patients ($P < 0.05$). The changes that did occur in these tests on the first postoperative day reverted to baseline levels thereafter. There were no significant changes in the remaining two tests, the Mini Mental State Test or the Digit Span Test, at any time in either group. We conclude that postoperative mental deterioration is no greater in elderly than in young patients.

Key Words: AGE FACTORS, POSTOPERATIVE MENTAL RECOVERY. PSYCHOLOGIC RESPONSES, POSTOPERATIVE—age.

Advances in surgical and anesthesiological techniques have made operations more feasible, safer, and more frequent. Consequently, a higher number of operations are performed on the elderly population. Although the risk has diminished, major surgery is still associated with significant postoperative morbidity and mortality (1). Psychological problems, in particular preoperative anxiety and postoperative confusion, contribute to the postoperative morbidity (2). The frequency of postoperative delirium in patients with femoral neck fractures approaches 50%, and results in four times longer in-hospital stays (3).

The factors said to predispose the elderly to delirium include aging processes in the brain, structural brain disease, a reduced capacity for homeostatic regulation and hence for resistance to stress, and impairment of vision and hearing (4). A high prevalence of chronic diseases and age-related changes in the pharmacokinetics and pharmacodynamics of drugs, and relocation to an unfamiliar environment such as a hospital, are also said to contribute to the development of delirium (4).

The duration of stay in hospital after a general anesthetic for an elective cholecystectomy has recently been decreasing without markedly increasing the risk to the physical safety of the patient (5). However, the available data on the recovery of patients after anesthesia have not addressed the issue of the relative rate of cognitive recovery after general anesthesia in elderly and in young patients (6–9). We therefore undertook a study to determine the incidence and duration of cognitive impairment for a period of 1 mo after elective cholecystectomy. We correlated the degree of cognitive impairment, if present, with age, sex, premorbid mental function, and postoperative medications.

Methods

This study was approved by the Hospital Ethical Committee. Informed consent was obtained from 40 patients scheduled for elective cholecystectomy, ranging in age from 25 to 83 yr. Patients with a history of visual or neuromuscular deficits, or major psychiatric disorders, were excluded from the study.

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Preoperative Assessment

Clinical and demographic data together with medical, surgical, and social histories, and medications used, were recorded. Hemoglobin, blood sugar, serum electrolytes, and arterial blood gas tension were measured preoperatively. The anxiety experienced by each patient about his or her forthcoming operation was assessed using a linear visual analog scale from 0 to 10 (0 = no anxiety, 10 = maximal anxiety). A battery of mental function tests was administered to define preoperative cognitive function in each patient. These tests include:

The Mini Mental State Test. This test includes 11 tasks that assess basic orientation, language, short-term memory, ability to calculate, and visuomotor ability. It is a sensitive and specific screening instrument for the presence of dementia or delirium (10) and was used in this study to exclude patients in a demented or confusional state as defined by a preoperative score of less than 24. The Mini Mental State Test was administered preoperatively for selection purposes and postoperatively as a check for anesthesia-induced delirium. Anthony et al. (10) found the test was 87% sensitive and 82% specific in detecting dementia and delirium.

The Symbol Digit Modalities Test (Digit Symbol Test). This test is sensitive to central nervous system disruption (11). It requires the patient to integrate visual scanning speed with substitution of numbers for symbols. It is well adapted to bedside administration. The patient is allowed 90 s to complete as many of the 110 symbol-to-number substitutions as possible, using a code provided at the top of the test page. A sensitivity of 86% using a cut-off point of 1.5 standard deviations (SD) below the mean for a variety of age groups has been reported (12).

The Digit Span Test. A well-recognized measure of attention span, this test requires the accurate repetition of verbally presented random number strings both forward and backward. From memory, the subject must repeat number sequences of increasing length until two consecutive number strings are repeated incorrectly. This process is repeated with a different set of numbers recited from memory in reverse sequence to their original presentation, until two number strings are again failed. Unlike the Digit Symbol Test, where the test code is available at all times, Digit Span testing requires one to hold information in the short-term memory and maintain it in an ordered sequence.

The Trail Making Test. This test is the most complex of the tests because it requires the simultaneous integration of several cognitive functions combined with a motor response. It is highly sensitive to the effects of brain dysfunction (11). There are two parts to the test. Part A requires the subject to sequentially connect the numbers 1–25, randomly displayed on a page, as quickly as possible. Part B mixes the numbers 1–13 and the letters A–K on the test page. The subject must connect the symbols in an ordered sequence by consecutively alternating the number-letter sets as quickly as possible. This test is scored by the number of seconds required to complete the task. The subject is alerted to any errors and the mistake is corrected. The timing is not stopped during the correction of mistakes.

Because the motor requirements for part A and part B are equivalent, part A serves as a control for the ability of the subject to physically perform the task. Cognitive efficiency, in terms of visual search strategies combined with speed and accuracy of mental set alternation, was therefore obtained by subtracting the results of part A from those of part B.

Mental function testing was performed the day before surgery to exclude any individual with preoperative dementia. The entire battery of tests were repeated on days 1, 2, 3, 4, and 30 postoperatively, using alternate forms of the Digit Span Test and the Trail Making Test to minimize practice effects.

Intraoperative Management

The type and quantity of anesthetic medications received during the general anesthetic and the duration of surgery were recorded for all patients studied. If possible, premedications were not given. However, if the patients were very anxious, they were given a premedication consisting of intramuscular (IM) meperidine (0.5–1 mg/kg) and promethazine (0.25–0.35 mg/kg). Anesthesia was induced with a sleep dose of 2–5 mg/kg thiopental and 1–2 μg/kg fentanyl, with precurarization using 3 mg of *d*-tubocurarine followed by muscle relaxation with 1.5 mg/kg of succinylcholine for tracheal intubation. Anesthesia was maintained using nitrous oxide/oxygen (2:1) in a semi-closed system with intermittent positive pressure ventilation. Increments of nondepolarizing muscle relaxants and fentanyl were given as required. Volatile agents (isoflurane or enflurane) were also added to the anesthetic regimen and were titrated to hemodynamic requirements. The end-tidal volatile anesthetic agent concentration was allowed to decrease to zero before extubation. Postoperatively, muscle relaxation was reversed with 5 μg/kg glycopyrrolate or 2 μg/kg atropine plus 50 μg/kg neostigmine. Meperidine (50–75 mg IM every 4–6 h as necessary) was given for postoperative pain control.

Postoperative Assessment

Routine blood tests and a blood gas analysis were repeated on the first postoperative day. All four mental function tests were repeated daily for the postoperative days 1, 2, 3, and 4, and on day 30. The visual analog anxiety scale was repeated on the fourth postoperative day to estimate residual anxiety levels about possible misfortunes, which may affect psychomotor testing. The time taken for the patient to ambulate, including the ability to visit the washroom unaided, the time of hospital discharge, and any untoward postoperative events were recorded.

Statistics

The Mini Mental State Test, Digit Span Test, and the Digit Symbol Test were scored by the number of correct responses. For these tests, a higher score is a better performance. Entry into the study required a Mini Mental State score above 24, restricting the range of possible scores to between 24 and 30. In contrast, scores of the Digit Span Test could range from 0 through 28; the upper limit of the Digit Symbol Test was 110. For these two tests, performance could be assessed using each patient as his or her own control or by comparing scores with standardized norms for individuals of the same age in the community (12,13). Scores on the Trail Making Test were a function of the time required to complete the tasks. In this case, a lower score is a better performance and the possible range of scores is unlimited. Patients served as their own controls. Standardized age-related norms are also available (14). Chi-square tests, Student's *t*-tests, one-way analysis of variance for repeated measures, and multiple regression analysis were used for the statistical analysis of data; the results were presented as mean ± SEM. A P value ≤0.05 was considered to be statistically significant.

Results

The study patients were allocated into two groups, those greater than 60 yr of age (60+) and those less than 60 yr of age (<60). There were 15 patients in the 60+ group (mean, 67.0 ± 1.7 yr) and 25 in the <60 group (mean, 39.7 ± 2.0 yr). The distribution of patient ages is shown in Figure 1. There were no significant differences between the two groups with regard to sex, weight, smoking, alcoholic intake, or duration of surgery. The elderly patients had a higher prevalence of medical and surgical problems and took a greater number of daily medications (Tables 1 and 2). The ASA physical status classification also showed significant differences with a larger percentage of patients in the 60+ group being classified as ASA II, whereas the <60 group were predominantly ASA I.

There were no statistically significant differences in the dose of anesthetic agents between groups (Table 3). Intraoperatively, both groups of patients received volatile agents, either isoflurane or enflurane. The MAC-hour amounts of volatile agents given were not recorded, but all patients who received either of the volatile agents were extubated only when their end-tidal anesthetic gas concentration was zero. This was done to eliminate possible bias between those patients who were given volatile anesthetics and those who were not.

There was a trend toward higher postoperative analgesic and sedative requirements (meperidine, dimenhydrinate, or lorazepam) in the <60 group for both dose and duration of administration, but this did not reach the level of significance (Table 4). No differences were found between the two groups in visual analog anxiety rating by patients, either preoperatively (60+ vs <60: 3.2 ± 0.8 vs 4.9 ± 0.6) or on the fourth postoperative day (0 vs 1.1 ± 0.6).

Laboratory investigations done preoperatively and repeated on the first postoperative day showed a significant decrease in the hemoglobin, sodium, and blood urea nitrogen levels in both age groups. There were no significant differences between the two groups in any of the test results (Table 5).

No significant inter- or intragroup differences were noted on the Mini Mental State Test. The baseline Digit Symbol Test (Figure 2) showed a significant intergroup difference. The mean scores were 36.2 ± 3.3 in the 60+ group and 46.6 ± 2.8 in the <60 group ($P < 0.03$). This difference is within the normal range when corrected for age. No postoperative intergroup differences in the Digit Symbol Test scores were noticed when corrected for baseline differences. Within-group comparisons showed a deterioration in scores in both age groups on day 1 (60+, $P < 0.004$; <60, $P < 0.05$) and a return to baseline performance by day 2.

The Digit Span Test showed neither significant difference between the two groups on any of the days tested nor any postoperative deterioration. The difference between the results of part A and part B in the

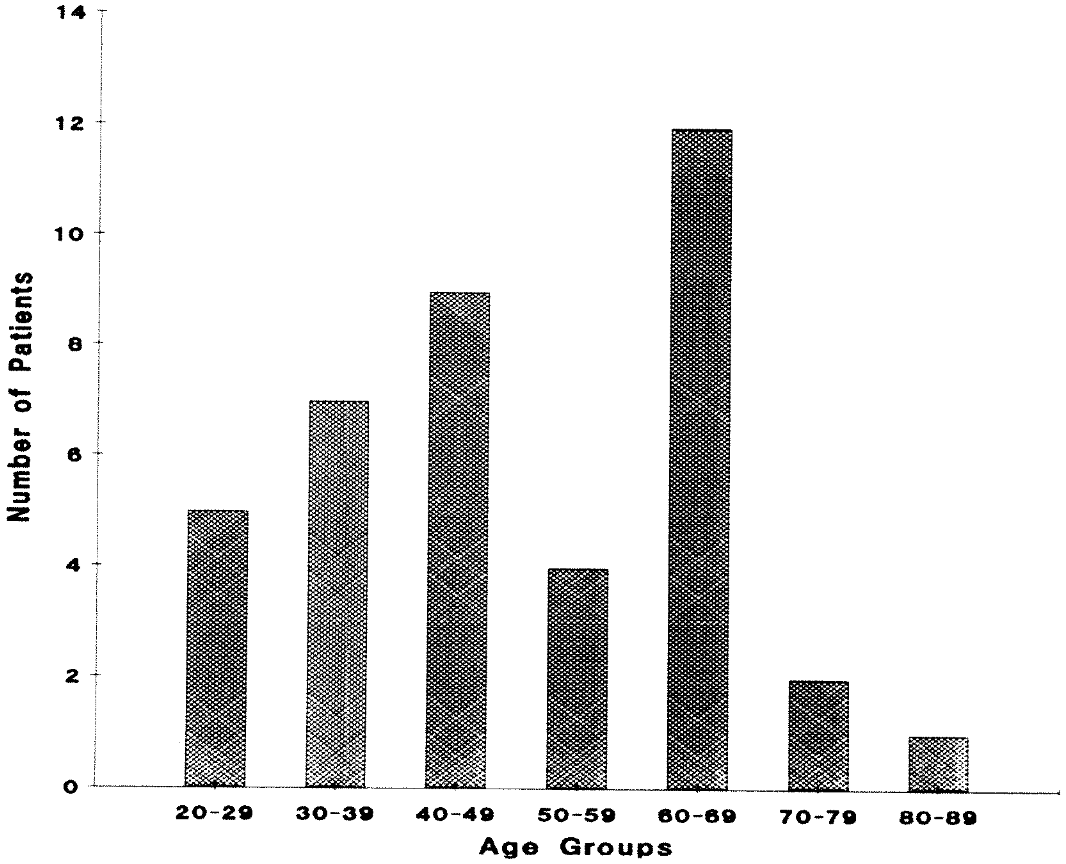

Figure 1. Distribution of patient ages.

Table 1. Demographic Data

	60+ (n = 15)	<60 (n = 25)
Age (yr)	67.0 ± 1.7[a]	39.7 ± 2.0
Weight (kg)	65.1 ± 2.5	66.2 ± 2.8
Sex (M/F)	4/11	8/17
Duration of surgery (min)	93.0 ± 9.2	85.3 ± 7.1
Daily medications (yes/no)	11/4	6/19[b]
ASA (I/II)	4/11	23/2[b]

60+, patients aged 60 yr and over; <60, patients aged less than 60 yr.
[a] Mean ± SEM.
[b] $P < 0.03$.

Trail Making Test was used to compensate for age-related changes in motor ability and therefore detects only cognitive impairment (Figure 3). There was no baseline difference, but significant postoperative impairment could be demonstrated even when standardized for age. The decrease in Trail Making Test performance on day 1 was significantly greater in the 60+ group than in the <60 group ($P < 0.02$). Repeated measures analysis of variance showed a postoperative decrease in performance only in the elderly patients ($P < 0.03$). The time taken for patients to become ambulatory and the time to discharge from hospital were not significantly different in the two age groups.

One patient showed periods of clinical confusion in the early postoperative period, accounting for an incidence rate of 2.5% in clinical confusion in the 40 patients with a 6.7% incidence among the 15 elderly patients. This patient, a 60-yr-old woman, had a past medical history of chronic bronchitis, sinusitis, peptic ulcer disease, and arthritis. Medication on admission consisted only of theophylline (300 mg twice a day).

Table 2. Preoperative Daily Medications

	60+ (%) (n = 15)	<60 (%) (n = 25)
Adrenergic β-blocking agents	8	4
Analgesics	20	4
Antidepressants	0	4
Benzodiazepines—hypnotics	4	0
Bronchodilators	8	4
Calcium channel blockers	4	0
Diuretics	12	0
Histamine H_2-receptor antagonist	4	4
Miscellaneous gastrointestinal drugs	4	4
Potassium supplements	12	0

Table 3. Intraoperative Medications

	60+	*n*	<60	*n*
Premedication (yes/no)	9/6		17/8	
Benzodiazepine (%)	40		44	
Analgesic (%)	27		36	
Antihistamine (%)	20		16	
Fentanyl (μg)	146.7 ± 25.2[a]	15	149.0 ± 14.6	25
Thiopental (mg)	268.3 ± 16.1	15	303.0 ± 19.3	25
Atropine (mg)	0.90 ± 0.11	8	0.99 ± 0.12	10
Glycopyrrolate (mg)	0.53 ± 0.07	3	0.70 ± 0.26	8
Neostigmine (mg)	2.50	7	2.50	15
Isoflurane (yes/no)	10/5		11/14	
Enflurane (yes/no)	5/10		9/16	

[a] Mean ± SEM.

Table 4. Postoperative Medications

	60+	*n*	<60	*n*
Meperidine (mg)				
Day of operation	130.8 ± 15.0[a]		148.9 ± 14.7	
Day 1 PO	291.1 ± 32.8		376.0 ± 35.7	
Day 2 PO	168.8 ± 30.5		228.6 ± 36.0	
Day 3 PO	150.0 ± 31.6		246.4 ± 84.2	
Day 4 PO	0		50.0	
Total	562.5 ± 64.0	14	781.0 ± 87.3	25
Dimenhydrinate (mg)				
Total	70.0 ± 20.0	5	103.3 ± 23.6	15
Lorazepam (mg)				
Total	3.3 ± 0.7	6	2.8 ± 1.0	5

PO, postoperatively.
[a] Mean ± SEM.

Table 5. Laboratory Data

	Preoperatively	Postoperatively
60+		
Hemoglobin (g/L)	133.1 ± 3.7[a]	121.1 ± 3.7[b]
Sodium (mEq/L)	142.7 ± 0.9	135.2 ± 1.1[b]
BUN (mEq/L)	6.1 ± 0.6	4.0 ± 0.8[b]
Blood gases		
pH	7.42 ± 0.01	7.42
Po$_2$ (mm Hg)	72.0 ± 3.5	66.0
Pco$_2$ (mm Hg)	42.2 ± 1.9	43.0
HCO$_3$ (mEq/L)	27.4 ± 1.0	27.0
<60		
Hemoglobin (g/L)	130.6 ± 2.6	125.0 ± 2.3[b]
Sodium (mEq/L)	141.8 ± 0.7	135.8 ± 0.4[b]
BUN (mEq/L)	4.9 ± 0.3	2.8 ± 0.3[b]
Blood gases		
pH	7.41 ± 0.01	7.40 ± 0.01
Po$_2$ (mm Hg)	82.4 ± 4.0	73.1 ± 4.8
Pco$_2$ (mm Hg)	41.8 ± 1.4	44.3 ± 1.6
HCO$_3$ (mEq/L)	26.2 ± 0.8	27.4 ± 0.90

[a] Mean ± SEM.
[b] $P < 0.001$.

She developed wound sepsis postoperatively; this required antibiotics and drainage. Her arterial blood gas tensions were within normal limits pre- and postoperatively. The patient was discharged in good condition on day 7. Her baseline mental function tests were normal except for her Digit Symbol Test, which was below the 95th percentile for her age. Postoperatively, the Trail Making Test, both parts A and B, deteriorated to below the 95th percentile; the Mini Mental State and Digit Symbol Tests also showed low scores. Only the Digit Span showed average scores. All the abnormal test results returned to the normal range by day 3.

Discussion

Discharge within 24 h after elective operations, especially minor surgical procedures, is a common occurrence. Moderate to major surgery is usually followed by a longer convalescence in hospital. Ideally, two basic factors should be considered in selecting patients for discharge: first, the surgical wound and the physiologic condition of the patient, and, second, the measurable psychomotor recovery of the individual. Surgical recovery is usually clinically evident, whereas psychomotor recovery may be more subtle and may be age-dependent. Age has been suggested as a predictor of longer and more serious cognitive loss (15). This study was therefore conducted to determine the speed of recovery and to see whether age would be a predictor of cognitive loss.

Our results show a deterioration in the Digit Symbol Test on the first postoperative day in both the young and the elderly patients and a deterioration in the Trail Making Test in only the elderly population in the same time period. All test scores were within normal baseline values by the second postoperative day and remained so thereafter. There were no changes found in either the Mini Mental State or the Digit Span Tests in either group. Only on the first postoperative day was there a significant difference present between the young and the elderly groups, and this occurred only in one of the four mental function tests.

These results are very encouraging and indicate that there may not be a major difference in cognitive recovery between the elderly and the younger patients even though the elderly are said to be more susceptible to the development of psychomotor stress, especially to deficits in orientation and memory (16).

Many factors have been postulated as possible causes for a supposed increase in susceptibility of cognitive dysfunction in the elderly (17–19). Old age leads to a reduced renal clearance of pharmacologic

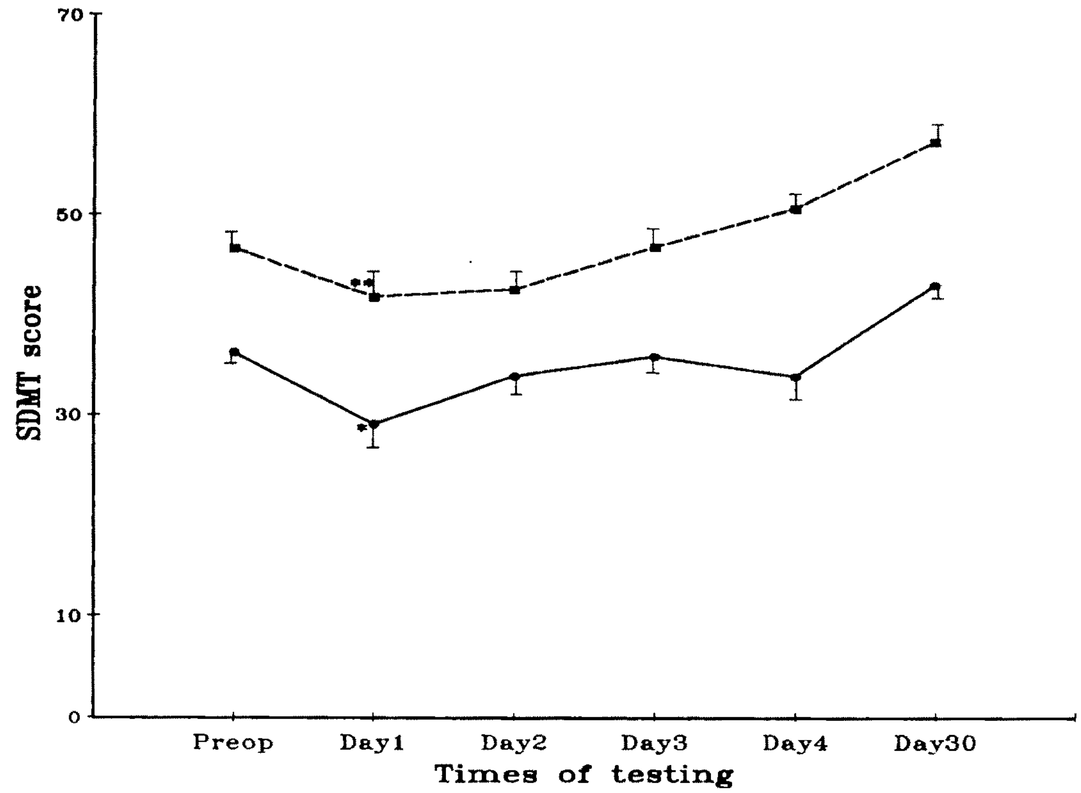

Figure 2. Comparison of the Symbol Digit Modalities Test (SDMT) scores (mean ± SEM) among patients ≥60 yr (●——●) and those <60 yr (■——■). *Statistically significant change within 60+ group on day 1 ($P < 0.004$). **Statistically significant change within <60 group on day 1 ($P < 0.05$).

agents (20) and thus to an enhanced deleterious effect on cognition. Advancing years also decreases the capacity of the liver to biotransform some drugs, reducing drug clearance and increasing the elimination half-life (17,21,22). Furthermore, the percentage of body weight composed of adipose tissue also increases with advancing age, and this may increase the volume of distribution and elimination half-life for the lipid-soluble drugs with proportionately greater and longer pharmacologic effects (17,23). All of these physiologic changes along with the trauma of surgery itself, and its associated fatigue, could supposedly contribute to a decreased performance on mental function tests after general anesthesia in the elderly population.

In this study, the elderly do not have an appreciably greater mental deterioration postoperatively than do young patients. Thus, hypothesizing postoperative mental dysfunction on theoretical grounds may not have clinical significance. Bed-rest, sleep deprivation, caloric restriction, and sedation have all been implicated in the causation of postoperative fatigue and impairment in perception and psychomotor skills (24). The development of postoperative fatigue could equally well affect the young as well as the elderly and could subsequently lead to a deterioration of the psychomotor tests in both age groups on the first postoperative day.

In addition, Simpson et al. (25) showed that atropine made a difference regarding recovery of cognitive function after general anesthesia. In our study, eight patients in the elderly group, and 10 patients in the younger group received atropine. This may have accounted partially for the deterioration in mental function testing observed equally in both age groups on the first postoperative day.

Edwards et al. (26) found a progressive impairment in mental function postoperatively from days 2 through 7, being maximal on days 4 and 5. He did not test the patients on day 1. Reaction time, finger tapping, and symbol recognition were used. A disadvantage with these tests is the amount of motor control required, making it difficult to test patients on day 1. Another earlier study, by Rollason et al. (27), indicates a postoperative decrease in mental function only on day 5. A battery of eight time-consuming, nonbedside tests were used preoperatively, at 5 days and 6 wk postoperatively. Our results show a dissimilarity when compared with both of the above, in that our patients have an impairment only on the first

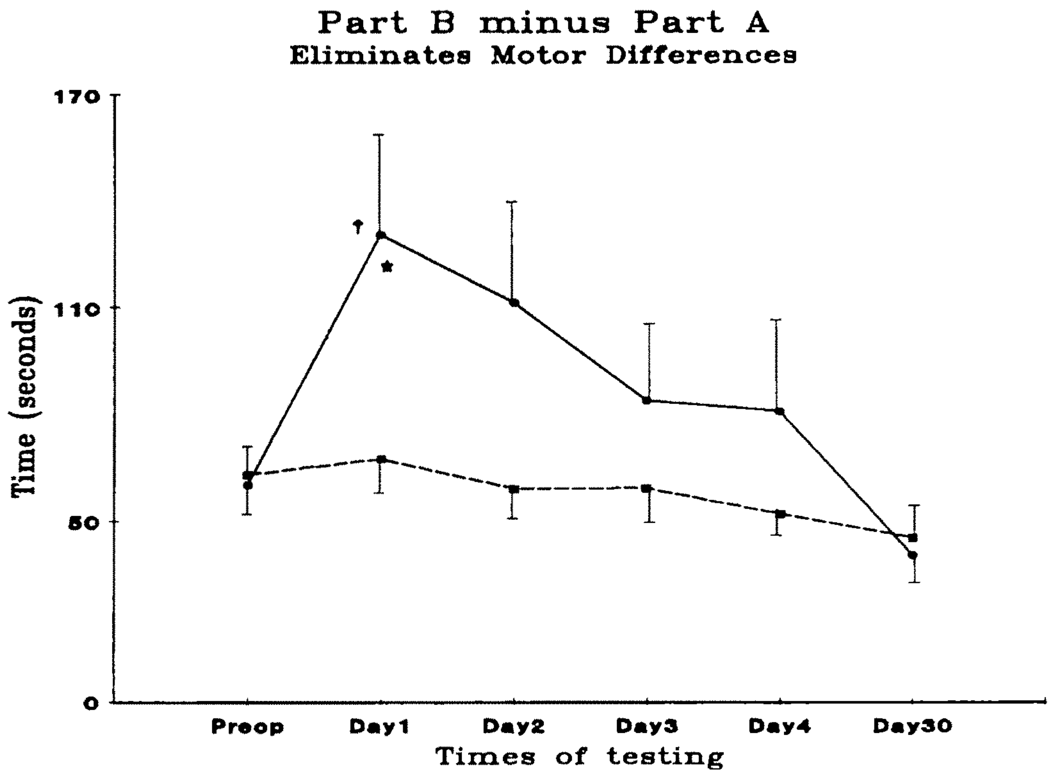

Figure 3. Comparison of the time taken to complete the Trail Making Test (mean ± SEM) in patients ≥60 yr (●——●) and those <60 yr (■——■). *Statistically significant difference between groups ($P < 0.02$). †Statistically significant change within groups ($P < 0.03$).

postoperative day. All are cognitively unimpaired from the second postoperative day onward. A possible, postulated reason is that medical practice has undergone changes in the last decade with more of an emphasis on early mobilization after surgery, caloric monitoring, and ensuring adequate sleep using better pharmacoactive sedative and analgesic medications with a reduction in the duration of the fatigue state.

Bedford (28) quotes an incidence of postoperative confusion as approximately 7% of 251 elderly patients who underwent surgical procedures ranging from prostatectomies to inguinal hernias to fractured femurs. This is comparable to our estimate of 6.7%. One patient in our study developed episodes of clinical confusion during the first postoperative day. Her dementia may have been due to the effects of wound infection with associated fever (24).

Our results do not preclude the possibility that the use of more sophisticated and sensitive tests may be able to define a greater age-related cognitive recovery after general anesthesia. In a pilot study that we undertook, we used several other complicated psychomotor tests in addition to the four mental tests used in this study. We found that a large percentage of patients refused or were unable to do the complicated psychomotor tests.

In conclusion, we have demonstrated the presence of postcholecystectomy cognitive changes in the elderly population as reflected by altered scores on the Digit Symbol and Trail Making Tests, and cognitive changes in the young population as demonstrated by the Digit Symbol Test on the first postoperative day. Both the younger and the elderly populations suffer performance impairment on the first postoperative day, and the elderly do not have appreciably greater mental deterioration postoperatively than do young patients.

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Modulation of Pain-Related Somatosensory Evoked Potentials by General Anesthesia

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KOCHS E, TREEDE RD, SCHULTE AM ESCH J, BROMM B. Modulation of pain-related somatosensory evoked potentials by general anesthesia. Anesth Analg 1990;71: 225–30.

The aim of the present study was to assess if late somatosensory evoked cerebral potentials (SEPs) in response to painful electrical stimuli are a sensitive indicator for analgesic treatment during general anesthesia. For this purpose, a pain model developed for the quantification of drug-induced analgesia in awake volunteers was used in 10 patients scheduled for elective abdominal hysterectomy. Before induction of anesthesia, stimuli were adjusted to two and three times the pain threshold for each individual. Late auditory evoked potentials (AEPs, 30 dB hearing level) and spontaneous electroencephalogram were also evaluated. After control recordings, anesthetic treatments were varied in the following sequences: (a) 0.8% (end-tidal) halothane with 70% nitrous oxide (HN); (b) 0.8% halothane in oxygen (H1); (c) same anesthetic condition as in H1, but the SEP and AEP stimulus intensities were increased to 15 times pain threshold and to 70 dB hearing level, respectively (H2); and (d) fentanyl (0.25 mg) was given with 0.8% halothane in oxygen with no further change in stimulus intensities (HF). In treatments HN and H1, blood pressure and heart rate increases to pain stimuli were abolished, and SEPs and AEPs were both suppressed. Increasing the somatosensory stimulus intensity (treatment H2) stimulated heart rate and arterial pressure responses and again elicited the SEPs. However, AEP components remained suppressed with increased auditory stimulus intensity. Addition of fentanyl (HF) suppressed SEP amplitudes and stimulus-induced hemodynamic responses. Our results suggest that late SEPs in response to painful stimuli change with different analgesic levels.

Key Words: BRAIN, EVOKED CEREBRAL RESPONSES. BRAIN, ELECTROENCEPHALOGRAPHY.

General anesthesia can be monitored by several electrophysiologic parameters. The hypnotic effects of anesthetics can be assessed by processed spontaneous electrical activity of the brain (1–3). The degree of muscle relaxation can be quantitated by electromyographic techniques (4). Lack of analgesia, however, is grossly assessed by increases in blood pressure and heart rate. Monitoring techniques that specifically identify nociceptive activation would be important and clinically relevant (5).

In pain research, psychophysical techniques rely on communication with awake and cooperative subjects (6,7). An alternate approach utilizes late components of the somatosensory evoked cerebral potentials (SEPs) (8–11). Amplitude changes in pain-related SEPs have been validated as indicators of analgesia in awake human subjects (8,11,12). This was accomplished by correlating SEP amplitudes with variations in subjective pain ratings. These "pain-related" SEP components have quantified analgesic treatment efficacy, both of narcotic (13–15) and nonnarcotic analgesics (16). The aim of the present study was to investigate whether the analgesic component of general anesthesia can be assessed by neurophysiologic methods. For this purpose we used an experimental pain model that evaluates pain-related SEPs in response to intracutaneously applied electrical pulses (17).

Methods

Ten subjects (aged 38–57 yr, ASA physical status I or II) scheduled for elective abdominal surgery (hyster-

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ectomy, nonmalignant indications) were enrolled in the study. None of the patients had taken any centrally acting drugs for at least 3 mo before the study. They were free from neurologic or psychiatric disorders. In accordance with the Helsinki II declaration the study was approved by the local ethics committee; informed consent was obtained at the preanesthetic examination.

The electroencephalogram (EEG) and late cortical somatosensory (SEP) and auditory (AEP) evoked responses were continuously recorded by means of an EEG-amplifier (Biosignalverstaerker, nbn-electronics) from vertex (Cz) versus linked earlobes (A1-A2). For artifact control, the electrooculogram was recorded from supra- and infraorbital leads. For all recordings the filters were set at 0.5 and 30 Hz. The interelectrode impedances were kept below 5 kΩ (at 12 Hz). Stimulus onset and pre- and poststimulus EEGs were stored on analog tape (Store 7DS, Racal) and were digitized off-line (LSI 11/23, 100-Hz sampling rate).

Somatosensory stimuli were given to the tip of the left index finger by the intracutaneous technique described by Bromm and Meier (17). Briefly, the superficial epidermal layers of the glabrous skin are carefully removed, and weak constant current stimuli (200-Hz square waves, 20-ms duration) are passed through a metal electrode (diameter, 1 mm), with a large return electrode placed at the middle finger. This procedure ensures a high current density at the superficial, predominantly nociceptive nerve terminals. As a consequence, pain thresholds with this technique are one order of magnitude lower than with conventional electrical skin stimuli (17). The sensation elicited is described as a stinging pain similar to that evoked by dental stimuli. Detection and pain thresholds were determined after premedication. The interstimulus interval for the intracutaneous stimuli ranged from 10 to 20 s. Each electrical stimulus was followed by a binaurally applied auditory stimulus (500 ms, 1000 Hz, 30 dB hearing level [dBHL]) 3 s later (Figure 1). The auditory stimulus intensity (30 dBHL) was chosen according to normative data in healthy volunteers (17).

Analysis epochs for SEPs and AEPs were 500 ms each (Figure 1). Peak-to-peak amplitudes were determined for both modalities. The spontaneous EEG segment of 2.56-s duration preceding each somatosensory stimulus was also analyzed. Integrated power densities in selected frequency bands (δ: 0.5–3.9 Hz, θ: 4.0–7.4 Hz, α_1: 7.5–8.9 Hz, α_2: 9.0–12.4 Hz, β_1: 12.5–18.0 Hz) were calculated after Fast Fourier Transformation (Kaiser window, −40 dB sidelobe suppression) (18). Power densities of the spontaneous EEG and the responses of the evoked electrical brain activities were averaged over 40 trials (called one "stimulus block"). For the assessment of reliability, two separate stimulus blocks were analyzed for each condition investigated.

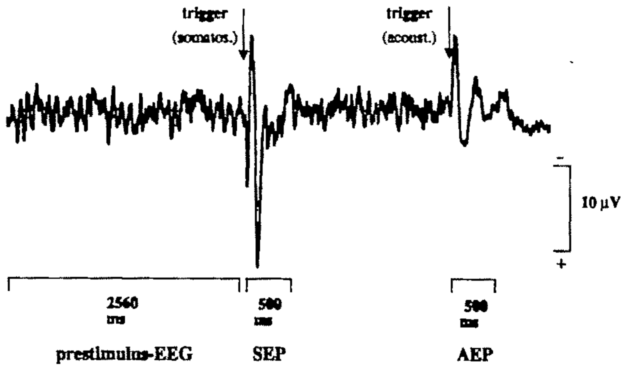

Figure 1. Original recording of one pre- and poststimulus EEG epoch in one subject. After recording of a prestimulus EEG segment (duration: 2.56 s), the electrical intracutaneous stimulus (trigger somatos.) for the recording of SEPs was applied. Auditory evoked potentials were elicited by an auditory stimulus (trigger acoust.) 3 s later. Analysis time for SEP and AEP was 500 ms each. The interstimulus interval for the SEPs was 10–20 s. Forty individual recordings were averaged for each "stimulus block" (see text).

Table 1. Experimental Protocol: Anesthetic Regimen and Applied Stimulus Intensities for Late Somatosensory and Auditory Evoked Potentials

Group	n	Stimulus intensities SEP (times pain threshold)	 AEP (dBHL)
C	10	2–3	30
HN	10	2–3	30
H1	10	2–3	30
H2	10	15	70
HF	7	15	70

All measurements were completed before surgery.

SEP, somatosensory evoked potential; AEP, auditory evoked potential; C, day of surgery after premedication with 5 mg midazolam IM and 0.5 mg atropine IM; HN, treated with 0.8% halothane with 70% nitrous oxide; H1, treated with 0.8% halothane in oxygen; H2, same anesthetic condition as in H1; HF, treated with 0.8% halothane in oxygen plus 0.25 mg fentanyl IV.

Table 1 summarizes the sequence of experimental conditions for each patient. The day before surgery, patients were familiarized with the experimental setup and procedure. On the day of surgery, patients were premedicated with midazolam (5 mg IM) and atropine (0.5 mg IM) 45–60 min before the start of the investigation. After determination of individual detection and pain thresholds, two stimulus blocks were recorded (control data: C). After this, anesthesia was induced with etomidate (0.3 mg/kg IV) and vecuronium (0.08 mg/kg IV). After tracheal intubation, anesthesia was maintained with nitrous oxide

(F_{IO_2} = 0.3, 6 L/min) and halothane (0.8%). Ventilation was adjusted to maintain end-tidal P_{CO_2} (Capnograph, Datex) between 35 and 40 mm Hg. The Einthoven lead I of the electrocardiogram (RM300, Honeywell), mean arterial blood pressure (Dinamap, Critikon), and end-tidal halothane concentration (EMMA, Engstroem) were monitored. During anesthetic levels of 0.8% halothane with 70% nitrous oxide (HN) and of 0.8% halothane in oxygen (H1), SEP and AEP stimulus intensities were two to three times the pain threshold and 30 dBHL, respectively. During treatments with 0.8% halothane in oxygen (H2) and 0.8% halothane in oxygen with 0.25 mg fentanyl (HF), SEP and AEP stimulus intensities were increased to 15 times the pain threshold and to 70 dBHL, respectively. All recordings were completed before the start of surgical procedures. In three patients, treatment HF could not be tested due to lack of time before the start of surgery. To assess stimulus-induced hemodynamic responses, heart rate (HR, averaged over 10 cycles) and mean arterial pressure (MAP) were recorded 1 min before and 5 min after the start of each stimulus block. Ringer's solution was infused to maintain MAP during anesthetic induction.

Data are reported as mean ± SEM. A one-way analysis of variance with repeated measures was used to analyze responses across anesthetic conditions. Post hoc comparisons were performed using Scheffé tests. Significance was assumed at $P \leq 0.05$.

Results

Cardiovascular Parameters

Heart rate and MAP increased during the stimulus blocks under control conditions (C). Induction of anesthesia resulted in a significant increase in HR, but electrical pain stimulation had no effect on hemodynamic variables during treatment HN (Table 2). Increasing stimulus intensity to 15 times pain threshold (H2) produced a significant increase in both HR and MAP compared to prestimulus recordings. Addition of fentanyl to halothane (HF) decreased HR and MAP to control levels and abolished the hemodynamic response to electrical stimulation.

Table 2. Systemic Parameters (mean ± SD): Heart Rate (HR), Mean Arterial Blood Pressure (MAP), and End-Expiratory Carbon Dioxide Tension ($P_{et}CO_2$) 1 Min Before and 5 Min After the Start of Each Stimulus Block

Condition	t (min)	HR (beats/min)	MAP (mm Hg)	$P_{et}CO_2$ (mm Hg)	n
C	−1	75 ± 13	81 ± 10	—	10
	5	86 ± 12^{a}	89 ± 11^{a}	—	
HN	−1	85 ± 16^{b}	77 ± 10	33 ± 3	10
	5	87 ± 15^{b}	76 ± 12	33 ± 3	
H1	−1	91 ± 17^{b}	83 ± 15	35 ± 4	10
	5	95 ± 15^{b}	86 ± 13	35 ± 4	
H2	−1	90 ± 18^{b}	84 ± 14	36 ± 4	10
	5	101 ± 17^{a,b}	94 ± 16^{a,b}	36 ± 4	
HF	−1	72 ± 14	81 ± 14	36 ± 4	7
	5	71 ± 13	80 ± 14	36 ± 5	

n, number of patients studied.
See Table 1 for abbreviation of conditions.
$^{a}P \leq 0.05$ versus corresponding prestimulus period.
$^{b}P \leq 0.05$ versus control (C) at $t = -1$ min.

Neurophysiologic Parameters

The mean detection threshold for intracutaneous stimuli was 0.16 ± 0.03 mA, and the mean pain threshold was 0.32 ± 0.04 mA. Figure 2 shows grand mean SEPs, AEPs, and EEGs; all waveforms were reproducible within each anesthetic condition (compare solid and dashed lines). In Figure 3, calculated parameters averaged over all subjects are given for the different anesthetic conditions. Control recordings of SEPs consisted of a large biphasic deflection with a vertex negativity at 150 ms (N150) and a vertex positivity at 250 ms (P250). The AEPs had a similar shape with an amplitude smaller than the SEPs. The latencies of the AEPs (N100, P200) were 50 ms shorter than those of the SEPs due to the shorter conduction distance. α-Waves of about 9.5 Hz were dominant in the EEG power spectrum. Somatosensory and auditory evoked potentials were abolished by halothane with and without nitrous oxide anesthesia (HN and H1, Figures 2 and 3). Increasing the stimulus intensity reestablished SEP to levels approximating control recordings (H2). In contrast, increased auditory stimulus intensity did not change AEP. Adding fentanyl to halothane (HF) again attenuated the SEP response. Combined administration of halothane and nitrous oxide (HN) abolished EEG α-wave dominance in all subjects. Activity in a broad frequency range of 7–14 Hz became dominant during halothane anesthesia (H1, H2, and HF) (Figure 2) without nitrous oxide. Increased stimulus intensity (compare H1 and H2) did not affect prestimulus EEG recordings. Fentanyl caused a small but not significant increase in δ activity and a decrease in β activity.

Discussion

One major goal of intraoperative EEG monitoring is to assess the "depth of anesthesia" (3,19,20). Even

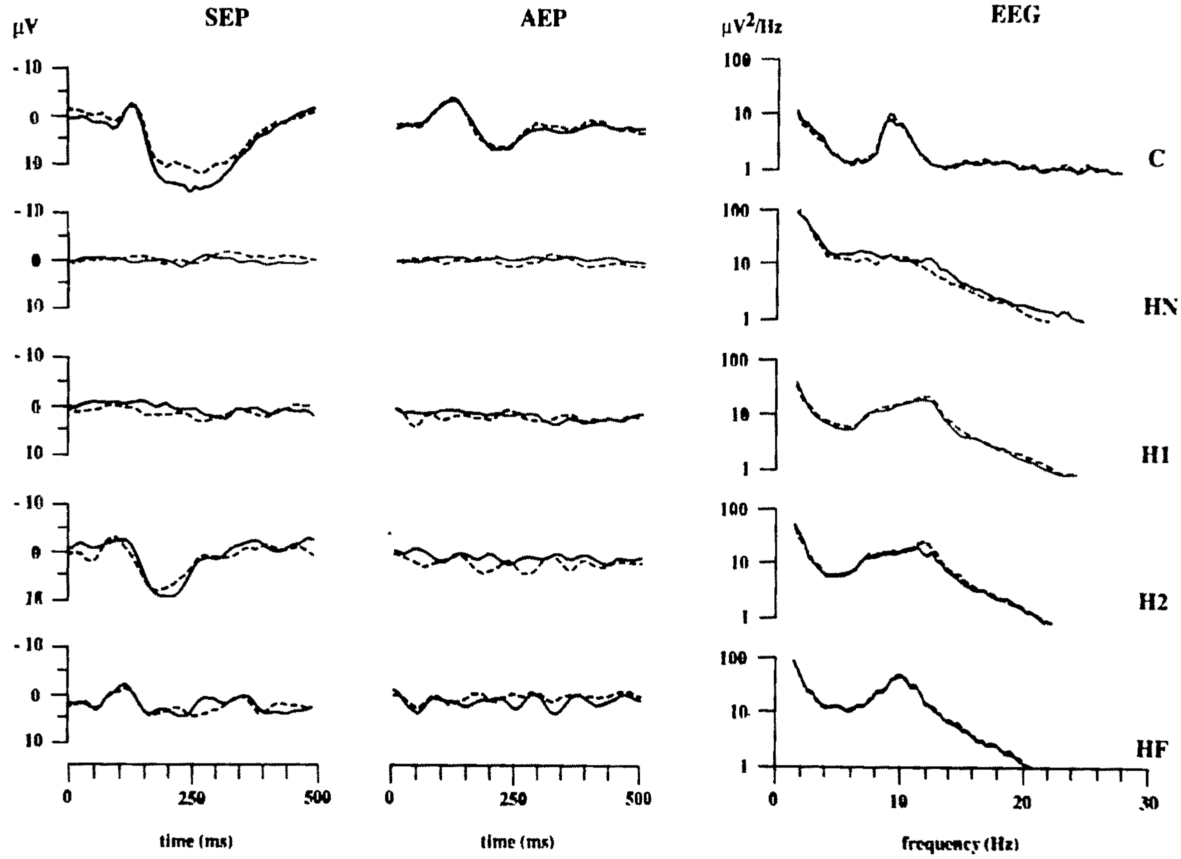

Figure 2. Effects of various anesthetic regimens on SEPs and AEPs, and on prestimulus EEG spectra. Two blocks of 40 peristimulus epochs (*solid and dashed lines*) were measured for each anesthetic condition (indicated on the right). Control ($n = 10$): after premedication with 5 mg midazolam IM. Second row: anesthesia with nitrous oxide and halothane (condition HN; $n = 10$) completely suppressed both SEP and AEP. Third row: no reappearance of SEP or AEP with lowered anesthetic depth (pure halothane anesthesia; condition H1; $n = 10$). Fourth row: increased stimulus intensity at the same anesthetic depth led to reproducible SEP, but AEP were still suppressed (condition H2; $n = 10$). Fifth row: the SEPs were attenuated after fentanyl administration (condition HF; $n = 7$) Vertex (Cz) versus linked earlobes (A1-A2) recording, negativity upward. All measurements were completed before the start of surgery.

though in a previous study (19) concurrent changes in EEG and hemodynamic changes following laryngoscopy and intubation have been shown, EEG may not be a sensitive indicator for analgesia during surgical stimulation because EEG and hemodynamic variables can vary independently (21). This was consistent with our results in which EEG monitoring showed little change in response to electrical pain stimulation. As an alternate approach we evaluated the effects of general anesthesia on late SEP in response to noxious stimuli and late AEP.

Both modalities of evoked responses were completely suppressed by nitrous oxide-halothane anesthesia. In previous studies, both halothane and nitrous oxide have been shown to reduce late cortical SEP (22,23). To separate the effect of nitrous oxide-halothane anesthesia from pure halothane anesthesia, nitrous oxide administration was terminated between treatment HN and H1. As a result, total EEG power decreased with a shift of the dominant activity into the α-band. However, SEPs and AEPs were still suppressed. This suggests that 0.8% halothane was sufficient to block subcortical and/or cortical sensory processing of pathways activated by weak nociceptive stimuli.

To simulate the surgical stimulus, somatosensory stimulus intensity was increased in treatment H2. This procedure increased the pain-related SEP components and hemodynamic responses to levels similar to those seen before induction of anesthesia and as reported in awake subjects (12,13,17,22). However, increased auditory stimulus intensity did not result in increased AEP components. This may be due in part to an inadequate match of SEP and AEP stimulus intensities at each anesthetic level. However, it is more probable that there are different anesthetic-induced effects on the auditory and somatosensory processing systems, be-

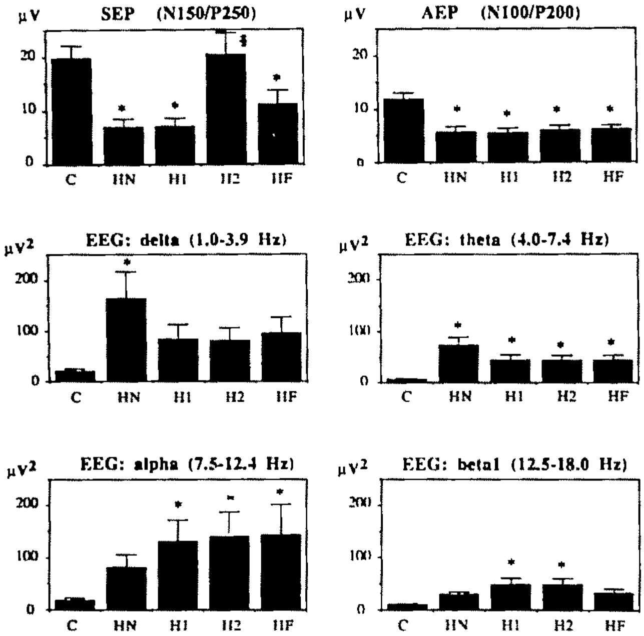

Figure 3. Effects of various anesthetic regimens on SEP, AEP, and EEG parameters. Late amplitude differences between N150 and P240 for SEP, N100 and P200 for AEP, and power densities in selected frequency bands of the spontaneous EEG were evaluated. The two stimulus blocks measured under each condition were combined into one bar. C: control recordings after premedication, before induction of anesthesia; HN: anesthesia with 0.8% halothane and nitrous oxide in oxygen ($F_{IO_2} = 0.3$); H1: anesthesia with 0.8% halothane in oxygen ($F_{IO_2} = 1.0$); H2: same anesthetic condition as in H1, but stimulus intensity for SEP and AEP increased; HF: same stimulus intensities as in H2, anesthesia: 0.8% halothane in oxygen ($F_{IO_2} = 1.0$) and analgesia with fentanyl (0.25 mg IV). C-H1: $n = 10$, HF: $n = 7$. $^*P < 0.05$ versus control. $\S P < 0.05$ versus H1 and HF.

cause the initial anesthetic regimen depressed both SEP and AEP to the same extent.

To investigate if these late SEPs seen under halothane anesthesia may be related to pain, their modulation by a narcotic analgesic was assessed. The amount of SEP suppression after fentanyl injection was comparable to findings with opioids in awake subjects (13–15,22). Although our data are consistent with the analgesic effect of fentanyl, there are other possible mechanisms for the SEP depression. Late SEP components are also subject to changes in vigilance and attention (24). Thus the decrease in late SEP could be due to an unspecific drug-induced sedative effect. However, shifting EEG activity to lower frequencies occurred in our patients only to a minor degree, suggesting no substantial increase in sedation after administration of fentanyl. From this we assume an analgesic drug effect as a major cause for the attenuation of SEP amplitudes after administration of fentanyl.

In conclusion, this paper demonstrates that late SEPs due to noxious stimulation can be recorded during inhalational anesthesia, and that they are sensitive to narcotic analgesic treatment. In contrast, EEGs and AEPs were unspecific in response to painful stimulation under halothane and halothane-fentanyl anesthesia. Future studies evaluating various anesthetic regimens will be needed to show whether changes in pain-related SEP correlate with manipulations of analgesic level. If proven valid, late SEP monitoring could be useful for the assessment of the analgesic component of general anesthesia.

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Reevaluation of Perioperative Myocardial Infarction in Patients With Prior Myocardial Infarction Undergoing Noncardiac Operations

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SHAH KB, KLEINMAN BS, SAMI H, PATEL J, RAO TLK. Reevaluation of perioperative myocardial infarction in patients with prior myocardial infarction undergoing noncardiac operations. Anesth Analg 1990;71:231–5.

We studied 275 patients with prior myocardial infarctions undergoing noncardiac operations to determine the incidence and outcome of perioperative myocardial reinfarction. Perioperative myocardial reinfarction developed in 13 patients (4.7%) of whom 3 (23%) died of cardiac causes. When time between prior myocardial infarction and the date of anesthesia was analyzed, the incidence of perioperative myocardial reinfarction was 4.3% at 0–3 mo, 0 at 4–6 mo, 5.7% at >6 mo, and 3.3% at an indeterminate exact interval. None of the variables analyzed showed any significant correlation with the rate of reinfarction. The urgency of operation and aortic or vascular procedures were the only variables that approached, but failed to achieve, statistical significance.

Key Words: HEART, MYOCARDIAL INFARCTION. RISK, MYOCARDIAL INFARCTION—perioperative. COMPLICATIONS, MYOCARDIAL INFARCTION—perioperative.

Myocardial infarction (MI) within a 6-mo period before noncardiac operation is considered to be one of the risk factors for development of perioperative myocardial infarction (PMI). The risk of PMI has been shown to be as high as 37% when the prior MI was within 3 mo and 16% when the prior MI was within a 4–6-mo period before noncardiac operation (1,2). In 1983, we reported a lowered incidence of PMI (<7%) in patients with recent MI undergoing noncardiac operations (3). We attributed this reduction in cardiovascular morbidity to various factors including preoperative optimization of the patient's status, aggressive invasive monitoring of the hemodynamic status, and prompt treatment of any hemodynamic aberration. We decided to follow up these results to determine if they stood the test of time.

Methods

Two hundred seventy-five patients with prior MI undergoing noncardiac operations were prospectively studied for the incidence and outcome of PMI after approval was obtained from the Institutional Review Board. A patient was considered to have previous MI if any of the following criteria was satisfied: clinical history of MI, documented electrocardiographic changes of MI, or appropriate cardiac enzyme studies that included creatinine kinase MB isoenzyme (CK-MB) and lactic dehydrogenase isoenzyme. Patients were divided into three groups depending on the interval between their most recent MI and the time of anesthesia (0–3 mo, 4–6 mo, and >6 mo). Patients with silent MI diagnosed by electrocardiographic criteria without a clinical history (presence of Q waves > 0.04 s and amplitude of Q wave > 1/3 the amplitude of R wave) were also included in the investigation as a separate group (group 4). The diagnosis of prior MI was made by cardiologists. All patients undergoing elective or emergency noncardiac operations during the 18-mo study were included in the investigation. Patients undergoing emergency operation for ruptured aortic aneurysm and patients requiring noncardiac operation to treat

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Table 1. Incidence of Perioperative Myocardial Infarction in Patients Who Underwent Noncardiac Operations

	Number of patients (% with PMI)				
Preoperative characteristic	Group 1 (0–3 mo)	Group 2 (4–6 mo)	Group 3 (>6 mo)	Group 4 (silent MI/age indeterminate)	Total
Age					
≥65 yr	14 (7.1)	10 (0)	117 (5.9)	41 (4.9)	182 (5.5)
<65 yr	9 (0)	8 (0)	57 (5.3)	19 (0)	93 (3.2)
Sex					
Male	13 (7.6)	14 (0)	133 (6)	33 (3)	198 (5.1)
Female	10 (0)	4 (0)	41 (4.9)	27 (3.7)	77 (3.8)
Emergency operation	13 (7.6)	3 (0)	17 (11.7)	10 (20)	43 (11.6)
Site of operation					
Abdominal	8 (0)	4 (0)	43 (7)	15 (6.7)	70 (4.3)
Thoracic	1 (0)	0 (0)	7 (0)	1 (0)	9 (0)
Aortic/PV	3 (0)	4 (0)	36 (16.6)	12 (10)	55 (10.9)
Other	11 (9)	10 (0)	88 (1.1)	32 (3.1)	141 (2.8)
Congestive heart failure	10 (10)	12 (0)	29 (0)	13 (7.6)	64 (3.1)
Hypertension	14 (0)	9 (0)	87 (8)	36 (2.8)	146 (5.5)
Anesthetic technique					
General anesthesia	16 (6.3)	10 (0)	115 (5.2)	47 (2.1)	188 (4.3)
Spinal/epidural	3 (0)	4 (0)	39 (7.6)	7 (14.2)	53 (7.5)
Regional block	0 (0)	1 (0)	8 (12.5)	2 (0)	11 (9)
Monitored anesthetic care	4 (0)	3 (0)	12 (0)	4 (0)	23 (0)
Total	23 (4.3)	18 (0)	174 (5.7)	60 (3.3)	275 (4.7)

PMI, perioperative myocardial infarction; PV, peripheral vascular.

the complications of cardiac operation (e.g., exploratory laparotomy for superior mesenteric artery thrombosis after cardiac operation) were not included in the study.

The following information was acquired and tabulated for all patients: age, sex, interval between the most recent MI and the date of anesthesia, site and duration of the operation, associated cardiovascular problems (e.g., congestive heart failure, hypertension, angina), associated medical problems (e.g., renal, hepatic, pulmonary), anesthetic drugs, monitoring, preoperative blood pressure reading and arrhythmias, preoperative use of vasodilator-vasopressor and inotropic drugs, and results of arterial blood gas tensions in the perioperative period. The clinical management of the patients was left to the discretion of the anesthesiologist. Each patient's daily course was followed up during the entire hospital stay.

Perioperative hypotension and hypertension were defined as a >30% change in stable preinduction blood pressure, sustained for a minimum period of 5 min. Perioperative myocardial reinfarction was diagnosed if the patient had either chest pain or electrocardiographic evidence of subendocardial or transmural MI. Either criterion had to be associated with a rise in blood levels of CK-MB isoenzyme of >10 IU/L by immunoinhibition/immunoprecipitation technique (0–10 IU/L is a normal range at our institution). The diagnosis of PMI was confirmed by an independent cardiologist not directly involved with the patient. Electrocardiograms were taken and CK-MB levels measured for three consecutive days and on the seventh postoperative day in all patients. Statistical differences in the frequency of occurrence of PMI in all four groups were sought using χ^2 analysis. Fischer's exact test was applied on variables with a small number of observations. A probability value of <0.05 was accepted as indicative of statistical significance.

Results

A total of 275 patients with previous MI were studied over a period of 18 mo. Comparison of perioperative patient characteristics in all four groups is shown in Table 1. There were no significant differences among all four groups for any variables analyzed. Perioperative myocardial infarction developed in 13 of the 275 patients (4.7%). Three of these 13 patients (23%) died of cardiac causes. Two more patients did not sustain a PMI but died of cardiac causes (e.g., arrhythmias or ventricular failure). Thus, a total of 5 patients (1.8%) died of cardiac causes. Of the 13 patients with PMI, transmural PMI developed in 7 patients, 2 of whom

(29%) died of cardiac causes. One of the 6 patients (17%) sustaining subendocardial PMI also died of cardiac causes. Six of 13 patients (46%) sustaining PMI did not complain of chest pain; but all 13 patients showed electrocardiographic changes and a rise in CK-MB isoenzyme in the postoperative period.

Age, Sex, and Reinfarction

The incidence of reinfarction was 5.5% (10/182) in patients 65 yr of age or older as opposed to 3.2% (3/93) in patients younger than 65 yr of age. Among the 198 male patients, the incidence of PMI was 5.1% (10/198) whereas in female patients it was 3.9% (3/77). Thus, the incidence of PMI was slightly lower in younger patients and in female patients, but these differences are not significant statistically.

Urgency, Site of Surgery, and Reinfarction

The incidence of reinfarction was 11.6% (5/43) in patients who underwent emergency operation as opposed to 3.45% (8/232) in patients who underwent elective operations. Patients who underwent operations for major vascular procedures (aortic and peripheral vascular) had the highest incidence of reinfarction (10.9%) compared with only 4.3% (3/70) in patients undergoing abdominal operations and 2.8% (4/141) in patients undergoing other operations (e.g., ears, nose, throat; orthopedic; eye; urologic). Nine patients underwent thoracic operation and none of them developed PMI. These differences were not significant. Thus, emergency operations and aortic or major vascular operations approached but failed to achieve statistical significance.

Anesthesia and Time Since Previous Infarction

Of 23 patients operated within 3 mo after their previous infarction, only 1 patient (4.3%) suffered a PMI whereas no PMI developed in the 18 patients who underwent noncardiac operations from 4 to 6 mo after their most recent infarction. The incidence of PMI was 5.7% (10/174) in patients whose previous infarction was more than 6 mo old. Of the 60 patients in group 4 with silent MI, PMI developed in 2 patients (3.3%). Thus, the incidence of PMI was not different in patients with recent MI compared with the incidence of PMI in patients with previous MI more than 6 mo old or in patients with silent MI.

Incidence of Death and Previous Myocardial Infarction

Three of 13 patients (23%) in whom PMI developed died of cardiac causes. Two additional patients did not develop PMI but died of other cardiac causes such as ventricular arrhythmias or ventricular failure. Thus, 5 of 275 patients (1.8%) died of cardiac causes. Six additional patients among the 275 patients died of noncardiac causes such as sepsis and malignancy after a prolonged hospital stay.

Previous Myocardial Infarction and Other Nonfatal Complications

Postoperative complications that did not result in death included oliguria in 2 patients and new congestive heart failure in 4 patients. Worsening of congestive heart failure developed in 14 of the 64 patients who showed signs of congestive heart failure in the immediate preoperative period. In 8 patients either chest pain or signs of ischemia on electrocardiogram developed that resolved and did not result in reinfarction. In 18 patients significant atrial or ventricular arrhythmias, e.g., new onset of atrial fibrillation, ventricular bigeminy, and ventricular tachycardia developed. One patient had a nonfatal pulmonary embolism. Sepsis developed in 5 patients but resolved with appropriate medical and surgical management. Thus, the incidence of serious complications that did not result in death was 21.5% (59/275).

Anesthetic Technique and Reinfarction

Of 188 patients who received general anesthesia, 8 (4.25%) had PMI. Perioperative myocardial reinfarction developed in 4 of the 53 patients (7.5%) having spinal or epidural anesthesia, 1 of the 11 patients having other types of regional anesthesia (9.1%), but in none of the 23 patients having monitored anesthesia care with supplemental intravenous sedation. These differences in the rate of PMI are not significant.

Postoperative Day of Reinfarction

Two of the 13 patients in whom PMI developed did so on the day of operation in the immediate postoperative recovery period (day 0). Reinfarction developed in 4 patients on the first postoperative day, in 4 on the second postoperative day, in 2 on the third postoperative day, and in 1 on the fourth postoperative day. Thus, reinfarction developed in 12 of 13 patients (92%) within the first three postoperative days and in 10 of 13 (77%) within the first 48 h of the postoperative period.

Intraoperative Hemodynamic Changes and Reinfarction

Four of the 20 patients (20%) in whom intraoperative hypotension developed and 2 of the 14 patients (14.3%) in whom tachycardia developed sustained PMI. One of the 35 patients in whom hypertension developed and none of the 3 patients in whom bradycardia developed suffered from PMI. Two of 18 patients in whom pulmonary artery occlusion pressure increased suffered PMI. Data on these intraoperative changes were collected from anesthetic records. No permanent strip chart recordings were obtained for later analysis.

Discussion

The risk of MI developing during the perioperative period is increased in patients with a history of prior MI. In 1972, Tarhan and associates reported a 6.6% incidence of PMI in patients with prior MI compared with 0.13% incidence of PMI in patients who never had prior MI (1). Topkins and Artusio also reported 10 times higher incidence of PMI in patients with prior history of MI (4). The risk of death is also much higher when MI occurs in the perioperative period instead of in a nonsurgical setting (2). These earlier reports have inspired several investigations of PMI incidence in patients with heart diseases undergoing noncardiac operations.

Previous investigators have shown that the more recent the MI, the greater the risk of suffering a PMI (1–4). The risk of PMI has been reported to be as high as 27%–37% when the operation is performed within the first 3 mo of MI and to be 11%–16% when the interval is 4–6 mo compared with around 5% incidence of PMI when the operation is delayed for more than 6 mo after MI (1,2). Goldman et al. also showed that a recent MI (less than 6 mo old) was a significant risk factor for prediction of postoperative cardiovascular morbidity and mortality (5). In 1983, Rao et al. showed that in patients with recent MI undergoing noncardiac operations, the risk of PMI can be reduced to around 5% whereas the same can be reduced to 1.5% when the prior MI is more than 6 mo old from the date of anesthesia administration (3).

Table 2. Comparison of Reinfarction Rate in Various Investigations

Duration of prior MI from the date of operation (mo)	Reinfarction rate (%)			
	Tarhan (1972)	Steen (1978)	Rao (1983)	Shah (1990)
0–3	37	27	5.8	4.3
4–6	16	11	2.3	0
>6	5.6	4.1	1.5	5.7
Age indeterminate		12		3.3

MI, myocardial infarction.

In the present report (Table 2), 23 patients underwent noncardiac operations within 3 mo of a prior MI and 18 patients underwent operations from 4 to 6 mo after a prior MI. The incidence of PMI in these patients was 4.3% (1/23) and 0% (0/18), respectively. This incidence is not different from the report of Rao et al. in 1983 but is significantly lower than the earlier reports of Tarhan and Steen and their associates (2,3). Thus, the present report confirms the findings of Rao et al. (3) that the risk of PMI in patients with recent MI can be reduced to around 5%. Rao et al. in their earlier report attributed this reduction in reinfarction to overall improved preoperative patient preparation, to improved intraoperative monitoring and aggressive management of hemodynamic changes, and to improved postoperative care in the intensive care unit. The present investigation did not make any attempt at finding the cause of reduction in the rate of reinfarction. Suffice it to say that our practices based on our earlier 1983 report have remained the same.

All previous investigators have shown that the risk of reinfarction decreases if the operation is delayed for 6 mo or more after a prior MI (1–3). In this report, the incidence of PMI in patients with prior MI more than 6 mo old was 5.7% (10/174), which is higher but not significantly different from the incidence of PMI in patients with recent MI. We would like to explain this apparent failure to show the reduction in the rate of reinfarction when the operation is delayed for more than 6 mo after the last MI. A close look at Table 1 will show that there were 55 patients with peripheral vascular disease out of a total of 275 patients who underwent aortic or other peripheral vascular operations. Thirty-six of the 55 patients underwent their aortic/peripheral vascular operation more than 6 mo after a prior MI and PMI developed in 6 of these 36 patients (17%). Jeffrey et al. and Domaingue et al. have shown that patients with peripheral vascular disease undergoing aortic operations are at a higher risk for cardiac complications to develop than are patients undergoing nonaortic operations (6,7). We are in agreement with their findings. Thus, the chance occurrence of having more patients undergoing aortic operation and sustaining PMI in group 3 (prior MI more than 6 mo old) in our study has skewed the results and has caused the apparent failure to show the further reduction in the reinfarction rate when the elective operation is delayed for more than 6 mo after prior MI. The rate of reinfarction in patients with prior MI more than 6 mo old would have been 2.9% (4/138) if only nonaortic/nonvascular operations were considered in this report. Based on this explanation, we still recommend that if the operation can be delayed, it would be advisable to wait for at least 6 mo before subjecting a patient to an elective major noncardiac operation after a recent MI.

Three of the 13 patients (23%) in whom PMI developed died of cardiac causes. This confirms the findings of earlier reports that the mortality from cardiac causes is high in patients who sustain reinfarction in the perioperative period (2,4). Also, reinfarction developed in 12 of 13 patients (92%) in the first 48 h, which again is in agreement with previous reports and emphasizes the need for continuing intensive monitoring and care in the first 48 h (1,4). The 21.5% incidence of nonlethal but serious complications is indicative of the fact that even though the risk of reinfarction has been reduced over the years, patients with prior MI are still at a high risk for suffering from other postoperative complications and should be cared for cautiously.

Tuman et al. reported that the choice of anesthetic agent had no effect on the outcome after coronary artery operation (8), and Slogoff and Keats found no effect of choice of primary anesthetic agent on the incidence of new ischemia in patients undergoing coronary artery operation (9). Our patients also had coronary artery disease, but unlike patients in these reports (8,9), our patients underwent noncardiac operations. We did not find any effect of choice of anesthetic technique (general anesthesia versus regional anesthesia) on the outcome of PMI in patients undergoing noncardiac operations.

We did not record hemodynamic changes on permanent strip chart recording, which limits the usefulness of comments on hemodynamic changes and the rate of reinfarction. With these reservations, we would like to point out that hypotension and tachycardia carried worse prognosis than did hypertension and bradycardia.

In conclusion, we report the outcome of 275 patients with prior MI who underwent noncardiac operations. The rate of reinfarction in patients with recent MI undergoing noncardiac operations was around 5%. We also report that the mortality from cardiac causes is 23% in patients who suffer from reinfarction. Of all the reinfarctions, 92% of them occurred in the first 48 h. Intraoperative hypotension and tachycardia had worse prognoses than did hypertension and bradycardia. Last, the choice of anesthetic technique had no effect on the incidence and outcome of PMI in patients undergoing noncardiac operations.

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Morphine and Fentanyl Anesthetic Interactions With Diazepam: Relative Antagonism in Rats

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KISSIN I, BROWN PT, BRADLEY EL, Jr. Morphine and fentanyl anesthetic interactions with diazepam: relative antagonism in rats. Anesth Analg 1990;71:236–41.

The anesthetic effects of morphine-diazepam and fentanyl-diazepam combinations as characterized by abolition of the movement response to noxious stimulation were studied in rats to test the hypothesis of antagonistic interactions between the components of these combinations. Noxious pressure on the tail was used to induce the response. Dose-effect curves were constructed for the drugs given alone and in combination. With the use of probit procedure ED_{50} values for single drugs and their combinations were determined, and the interactions were analyzed with algebraic (fractional) and isobolographic methods. It was found that both morphine and fentanyl have a less than additive (antagonistic) interaction with diazepam. In combination the sum of fractional doses was higher than a single-drug fractional dose, 1.67 versus 1.00 ($P < 0.05$) for morphine-diazepam and 1.61 versus 1.00 ($P < 0.05$) for fentanyl-diazepam. The observed antagonism is a relative one that does not increase the requirement for one agent upon the addition of another agent.

Key Words: ANALGESICS, MORPHINE, FENTANYL. HYPNOTICS, BENZODIAZEPINES—diazepam. INTERACTIONS (DRUGS), MORPHINE, FENTANYL, DIAZEPAM.

In rat experiments, the morphine-diazepam interaction in relation to the hypnotic effect results in a synergism that is pharmacodynamic in nature (1). The interaction of morphine with thiopental in relation to the hypnotic effect is synergistic (2) and, at the same time, antagonistic regarding movement in response to noxious stimulation (3). In rats, midazolam antagonized the analgesic effect of morphine, but to a lesser degree than did barbiturates (4). We suggest that, despite the very pronounced morphine-diazepam synergism (supraadditive interaction) in relation to hypnosis, the interaction of these two agents may be antagonistic (infraadditive) in relation to another component of anesthesia, the blockade of movement response to noxious stimulation. The aim of the present study was to define the type of interaction (supraadditive, additive, infraadditive) between morphine and fentanyl on the one hand, and diazepam on the other, regarding purposeful movement in response to noxious stimulation.

Methods

Experiments were performed on male Sprague–Dawley rats weighing 275–325 g. The protocol for this study was approved by the Institutional Panel on Laboratory Animal Care. As an end point, we used the blockade of movement to noxious pressure on the tail. Gross purposeful movement was considered a positive response; similar to the motor response used for determination of MAC, stiffening or hyperventilation was not considered. To provide the noxious pressure, the rat's tail was positioned on a Teflon platform, and a plate (0.7-mm edge) transmitting a pressure of 400 g was applied on the border between the distal and the third quarter of the tail for 30 s. The experiments were carried out in a clear chamber 30 × 25 × 40 cm into which oxygen was delivered (4 L/min). The rat's tail (for noxious stimulation) or hind leg (for injection into the saphenous vein) could be extended to the outside of the chamber through a slot. The animals were placed in the chamber 15 min before the first injections. Each animal was given one predetermined dose of an agent or a combination of

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Table 1. Doses of Morphine, Fentanyl, and Diazepam Administered in the Study

Series	Subseries	Morphine (mg/kg)	Fentanyl (μg/kg)	Diazepam (mg/kg)
Morphine-diazepam	A (Morphine) $n = 20$	0.3; 0.5; 1.0; 1.5	—	—
	B (Diazepam) $n = 20$	—	—	30; 35; 40; 50
	C (Combination) $n = 20$	0.4; 0.5; 0.7; 1.1	—	20; 25; 35; 55
Fentanyl-diazepam	A (Fentanyl) $n = 20$	—	1.0; 1.5; 4.0; 7.0	—
	B (Diazepam) $n = 20$	—	—	30; 35; 40; 50
	C (Combination) $n = 20$	—	1.1; 1.2; 1.3; 1.5; 1.7	25; 27; 30; 35; 40

agents, and only one painful stimulation was applied. Times between injections of agents and the test were based on the times to peak effect for these agents: 15 min for morphine, 5 min for fentanyl, and 3 min for diazepam. The peak times were chosen after preliminary experiments. In the combined drug experiments, each drug was injected separately to synchronize the occurrence of the peak effects. The following agents were used: morphine sulfate (Lilly), fentanyl citrate (Janssen), and diazepam (Hoffman-LaRoche). The agents or their combinations were injected intravenously, fentanyl and morphine over 15 s, diazepam over 60 s. The volume of injections was 0.3–0.8 mL.

Two series of experiments were performed: a morphine-diazepam and a fentanyl-diazepam series. In each series, the interaction between the agents was determined in two steps (5). First, dose-response curves were obtained and the ED_{50} values were calculated. Second, isobolographic (6) and algebraic (fractional) (7) analyses were used to characterize the type and degree of the interaction. These methods have been described in detail in a previous publication (1). In brief, dose-response curves were constructed for the drugs given alone or in combination: three dose-response curves (subseries A, B, and C) in each of the two series. Twenty rats were used in each subseries to determine a dose-response curve. Morphine-diazepam weight ratio for the combination was 1:50, and the fentanyl-diazepam weight ratio was 1:23,000 (equipotency for blockade of movement in response to noxious stimulation). The doses used in the study are given in Table 1.

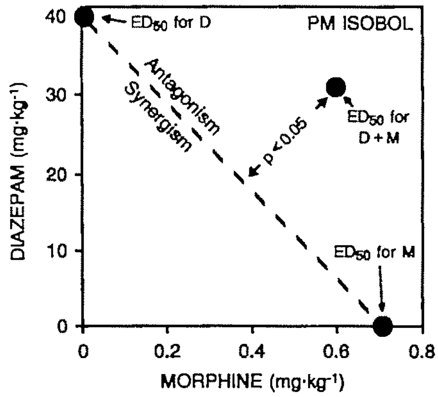

Figure 1. ED_{50} isobologram for the interaction of diazepam (D) and morphine (M) regarding abolition of purposeful movement (PM) in response to noxious stimulation.

ED_{50} values were obtained with the use of the probit procedure (8) and plotted in the form of an isobologram (Figure 1), with single-drug ED_{50} points placed on the dose coordinates of the isobologram and a combined ED_{50} point placed in the dose-field. The statistically significant deviation of the combined ED_{50} point to the right from an additive line (straight line joining single-drug ED_{50} points) was indicative of antagonistic interaction. The method of propagation of error (9), error estimates for ED_{50} points, and approximate t-test (10) were used to test the deviation of the combined ED_{50} point from the additive line. Algebraic (fractional) analysis was based on the expression of doses of the diazepam and morphine (or fentanyl) components of the combination as fractions of the doses of these drugs that produce the

Table 2. Morphine-Diazepam Interaction as Characterized by Abolition of Purposeful Movement in Response to Noxious Stimulation

	Equieffective doses (ED_{50}) $\frac{\text{Fraction}}{\text{mg/kg}}$			
Subseries	Morphine component	Diazepam compound	Sum of fractions	Coefficient of interaction[a]
A	$\frac{1.00}{0.69\ (0.31,\ 1.25)^b}$	0.00	1.00	—
B	0.00	$\frac{1.00}{41\ (36,\ 46)}$	1.00	—
C	$\frac{0.88}{0.61\ (0.50,\ 0.74)}$	$\frac{0.79}{32\ (26,\ 39)}$	1.67	0.60 $P < 0.05$

[a] Measure of interaction representing the ratio of the expected sum of fractions if the drugs are additive (i.e., 1) to the obtained sum of fractions. The P value denotes the significance of the difference from simple summation of the effects.

[b] 95% confidence limits are in parentheses.

same effect when given separately. In synergism, the sum of fractional doses is less than 1.0; in antagonism, it is more than 1.0 (7). Statistical validation for fractional (algebraic) analysis duplicated that for isobolographic analysis.

Results

The morphine-diazepam ED_{50} isobologram for blockade of movement in response to noxious stimulation is presented in Figure 1. The combined ED_{50} point deviates to the right from the additive line (joining single-drug ED_{50} points), indicating antagonism. Fractional (algebraic) analysis of this interaction is presented in Table 2. In combination, the sum of fractional doses is higher than a single-drug fractional dose (1.67 vs 1.00). As a result, the ratio of the expected sum of fractions if the interaction is additive to the obtained sum of the fractions (coefficient of interaction) is 0.60, indicating antagonism (coefficient is less than 1.0, $P < 0.05$). The fentanyl-diazepam interaction is presented in Figure 2 and Table 3. The outcome of the interaction is almost identical to that with morphine, which also indicates antagonism.

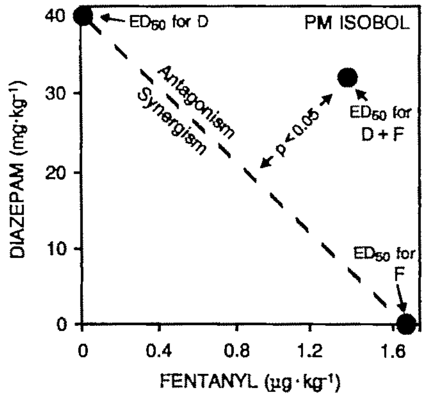

Figure 2. ED_{50} isobologram for the interaction of diazepam (D) and fentanyl (F) regarding abolition of purposeful movement in response to noxious stimulation.

Discussion

The algebraic (fractional) and isobolographic analyses used in the present study demonstrated antagonistic interactions of diazepam with morphine or fentanyl in relation to the prevention of movement in response to noxious stimulation. Antagonistic drug interactions can be divided into relative and absolute. With absolute antagonism, in contrast to relative, the requirement for one drug is increased by the addition of another drug. The morphine (fentanyl)-diazepam interaction resulted in the relative antagonism without increase in the requirement for one of the drugs to achieve the same degree of the effect. The benzodiazepine-opioid interaction in dogs has been studied recently by Schwieger et al. with the use of blockade of movement in response to noxious stimulation as an end point. They demonstrated antagonistic (less than additive) interaction between midazolam and fentanyl (11).

Morphine-diazepam interaction in relation to another end point of anesthesia, loss of the righting reflex, has the opposite outcome: very profound synergism (1). The same pattern of opposite changes regarding two different end points of anesthesia has been reported with thiopental-morphine (or fentanyl) combination (2,3). Table 4 summarizes these findings. The results may be explained by the hypothesis

Table 3. Fentanyl-Diazepam Interaction as Characterized by Abolition of Purposeful Movement in Response to Noxious Stimulation

	Equieffective doses (ED_{50})			
	Fentanyl component	Diazepam compound		
Subseries	$\frac{\text{Fraction}}{\mu g/kg}$	$\frac{\text{Fraction}}{mg/kg}$	Sum of fractions	Coefficient of interaction[a]
A	$\frac{1.00}{1.64\ (0.93,\ 2.88)}$	0.00	1.00	—
B	0.00	$\frac{1.00}{40\ (35,\ 48)}$	1.00	—
C	$\frac{0.84}{1.37\ (1.25,\ 1.51)}$	$\frac{0.77}{32\ (28,\ 34)}$	1.61	0.62 $P < 0.05$

Table 4. Morphine-Diazepam and Morphone-Thiopental Interactions in Relation to Two Components of Anesthesia: Hypnotic Effect and Loss of Movement in Response to Noxious Stimulation

	Combinations at ED_{50} level	
End point of anesthesia	Diazepam + morphine	Thiopental + morphine
Abolition of movement in response to noxious stimulation	Antagonism[a] CI = 0.6 $P < 0.05$	Antagonism (3) CI = 0.7 $P < 0.001$
Loss of righting reflex	Synergism (1) CI = 4.2 $P < 0.0001$	Synergism (2) CI = 2.3 $P < 0.001$

CI, coefficient of interaction, which represents the ratio of the expected sum of fractional doses of the drugs if they are additive (i.e., 1) to the obtained sum of fractional doses; CI > 1.0 in synergism, and CI < 1.0 in antagonism. *P*, significance of the difference from additive interaction.

[a] This study; references to the previous studies are given in parentheses.

that the anesthetic effect of an anesthetic is composed of several components (12–14), each with a different mechanism of action (loss of the righting reflex reflects one component of anesthesia, abolition of movement response to noxious stimulation reflects another). Because of the difference in the mechanisms of action, the combination of a benzodiazepine or barbiturate with an opioid can give opposite outcomes for two different components of anesthesia.

In our previous study on diazepam-morphine interaction (1), diazepam and morphine brain concentrations were determined when these two agents were given separately and in combination; no role for pharmacokinetic interaction was found. Additionally, with synergism between morphine and diazepam with regard to the hypnotic effect and antagonism between the same agents with regard to the motor response to noxious stimulation, pharmacokinetic factors probably do not play an important role in morphine-diazepam interaction.

Benzodiazepine and opioid receptors are pharmacologically separate. Morphine does not affect benzodiazepine receptors directly, as evidenced by the lack of changes in the affinity and density of the receptors (15). At the same time, morphine has an effect on the GABA receptor-ionophore complex where the benzodiazepine receptor is located. Morphine blocks the GABA-A receptor for which it has only moderate affinity (16–18). Thus, morphine in the central nervous system acts at two separate receptor sites: opioid receptors, which it activates at low doses (naloxone-reversible effect); and GABA-A receptors, which it blocks at relatively high doses (non-naloxone-reversible effect). The interaction of benzodiazepines and opioids at the GABA receptor-ionophore complex could lead to antagonism between diazepam (facilitating the action of GABA) and morphine (blocking the GABA receptor). However, it is difficult to explain why this antagonistic relationship at the GABA receptor level does not determine the outcome of the diazepam-morphine interaction for the hypnotic effect (which is profoundly synergistic).

It is now common practice to combine a benzodiazepine with an opioid to provide anesthesia. Human clinical experience and animal experimental data are difficult to correlate. At the same time, a high degree of opioid-benzodiazepine synergism for the hypnotic effect demonstrated in rats (1) was also confirmed in patients (19). The antagonistic effect of barbiturate on opioid-induced analgesia demonstrated in rat experiments was reported in patients with superficial anesthesia (20–22). It should be noted, however, that the antianalgesic effect of midazolam observed in rats (4) has not been reported in patients. Antagonistic interaction between opioids and midazolam regarding movement response to noxious stimulation can be easily overlooked in clinical practice for two reasons. First, morphine does not increase the diazepam requirement for blockade of the movement response; it can decrease the requirement, but only to a small extent. This is not an absolute antagonism that is relatively easy to notice, but a relative one when the sum of the fractional doses of two drugs is more than a single-drug fractional dose. Second, the morphine-diazepam anesthetic combination is commonly used with neuromuscular blocking agents. The myorelaxation can mask the antagonistic interaction for the movement response. Opioids (alfentanil) in subanalgesic doses can decrease by half the benzodiazepine (midazolam) requirement for induction of unconsciousness in patients (23). If the opioid-benzodiazepine antagonism observed in this study on rats is confirmed in patients, it would indicate that in anesthesia induced by benzodiazepine-opioid combinations, profound synergism regarding the hypnotic effect can coexist with antagonism in relation to the antinociceptive effect. Recent study by Hug et al. demonstrated that with high-dose lorazepam premedication and average plasma alfentanil concentration as high as 1178 ng/mL, in three out of six patients somatic motor responses to noxious stimulation were not suppressed (24). One can speculate that the insufficient suppression of the somatic motor responses in their study might be explained, at least in part, by antagonistic benzodiazepine-opioid interaction regarding antinociception.

In conclusion, interaction between morphine and fentanyl, on one side, and diazepam, on the other, regarding movement in response to noxious stimulation was found to be infraadditive (relative antagonism).

Appendix: Glossary

Absolute antagonism: drug interaction when the requirement for one agent to cause a certain effect is increased upon the addition of another agent.

Addition: type of drug interaction when a certain amount of drug A plus an equieffective amount of drug B evokes the same effect as the entire equieffective amount of drug A or drug B given alone.

Antagonism: type of drug interaction when the doses of interacting agents required for a certain effect are greater than those expected with additive effect.

Coefficient of interaction (CI): measure of interaction representing the ratio of the expected sum of fractional doses if the drugs are additive (i.e., 1) to obtained sum of fractional doses. CI is less than 1 in antagonism, and larger than 1 in synergism.

ED_{50}: intravenous dose required to abolish movement response to noxious stimulation in 50% of the population.

Fractional doses: doses of components of a combination expressed as fractions of the doses of the drugs (used as the components) that produce the same effect when given separately.

Isobol: a line on a dose-dose surface denoting dose combinations that elicit the same magnitude of response.

Relative antagonism: antagonistic drug interaction when the requirement for one agent to cause a certain effect is not increased upon the addition of another agent although the interaction is less than additive.

Synergism: type of drug interaction when the doses of interacting agents required for a certain effect are smaller than those expected with additive effect.

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1,4-Benzodiazepines Antagonize Opiate-Induced Antinociception in Mice

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ROSLAND JH, HOLE K. 1,4-Benzodiazepines antagonize opiate-induced antinociception in mice. Anesth Analg 1990;71:242–8.

The influence of diazepam, midazolam, and flunitrazepam on the antinociceptive effect of morphine, fentanyl, and buprenorphine was studied using the hot-plate test and the tail-flick test in mice. Diazepam and midazolam induced a dose-dependent attenuation of the effect of all three opiates in both tests of nociception. Flunitrazepam antagonized the antinociceptive effect only in the tail-flick test. The benzodiazepine effect could not be explained by altered tail-skin temperature. The antagonism did not correlate well with the sedative or muscle-relaxing properties of the benzodiazepines, and a different mechanism may therefore be involved. It is proposed that the antagonism represents an interaction between benzodiazepines and opioid systems in the brain participating in modulation of nociceptive inputs.

Key Words: HYPNOTICS, BENZODIAZEPINES—diazepam, midazolam, flunitrazepam. ANALGESICS, MORPHINE, FENTANYL, BUPRENORPHINE. INTERACTIONS (DRUG), BENZODIAZEPINES-ANALGESICS.

Diazepam and other benzodiazepines are frequently administered together with opiates to give better pain relief (1–3). Benzodiazepines induce sedation and muscle relaxation, reduce anxiety, and may also induce sleep, thus pain or painful procedures are better tolerated and the need for analgesics may be reduced (4,5). Benzodiazepines also have been reported to be of some value in the treatment of chronic pain (6).

The neurophysiological mechanisms of the benzodiazepine effect on nociception have been studied in animal models, but the conclusions often are conflicting (7–10). Studies in mice and rats indicate that benzodiazepines may either attenuate (7–9) or increase (11,12) the antinociceptive effect of morphine. Benzodiazepine antagonists have also been reported either to reduce the antinociceptive effect of morphine (13) or to induce antinociception (14). Benzodiazepine derivatives have been reported to bind to opioid receptors (15), but growing evidence links the interaction of benzodiazepines and opiates to benzodiazepine-receptor-mediated mechanisms (9,10,16).

Because benzodiazepines induce sedation and muscle relaxation, interpretation of the results in tests of nociception may be difficult. Because most pain tests in animals depend on a motor response, an apparent antinociception may instead be due to a reduced ability to perform the motor response. A test of sensorimotor performance may therefore be helpful to evaluate these possible motor effects.

We have previously shown that diazepam may antagonize the antinociceptive effect of morphine in the tail-flick test and the hot-plate test in mice (17). In the present work we studied the interactions between three different opiates and three different benzodiazepines using the hot-plate test and the tail-flick test in mice, with the aim of clarifying the mechanisms of these interactions. The study also includes a test for sensorimotor performance.

Materials and Methods

Animals

Male albino mice (Bom:NMRI) weighing 25–35 g were used in the experiments. The animals were housed in colony cages (16 mice in each) with free access to food and water before the experiments. They were maintained in climate- and light-controlled rooms (23 ± 1°C, 12/12-h dark/light cycle with lights on at 7 AM) for at least 2 wk before the experiments. Testing took

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place between 9 AM and noon. The animals were brought to the test room the day before testing and were thus adapted to the testing environment for at least 18 h. Two hours before testing, the animals were placed individually in standard macrolone cages (30 × 12 × 13 cm). Separate groups of animals were used for the different tests, and each mouse was used on one occasion only. All experiments have been conducted in accordance with the requirements set by the Norwegian Committee for Experiments on Animals.

Drugs and Route of Administration

Commercially available solutions of the following drugs were used: diazepam (Roche), flunitrazepam (Roche), midazolam (Roche), morphine hydrochloride (NAF laboratoriene A/S), fentanyl citrate (Janssen), and buprenorphine hydrochloride (Reckitt & Colman). All drugs were diluted in 0.9% NaCl to adjust the injected volume to 5 mL/kg. Diazepam, flunitrazepam, and midazolam were injected intraperitoneally (IP), and morphine, fentanyl, and buprenorphine were injected subcutaneously (SC) in the neck. All injections were made 30 min before testing, and in all experiments an equal volume of 0.9% NaCl was used as control for the injections.

Test for Sensorimotor Performance

To evaluate the muscle-relaxing and sedative effects of the benzodiazepine drugs, the mice were tested on a rotarod (18). A horizontal wooden rod, 50 cm long, 4.2 cm in diameter, and 100 cm above the floor, was driven by a motor. The speed of the rod was set to 2 cycles/min. With this speed, 90%–100% of control mice balanced on the rod for 45 s, which was the cutoff time.

Nociceptive Assays

Tail-flick test and tail-skin temperature registration. Tail-flick latency (19) was measured using an IITC Inc. model 33 Analgesiameter. Radiant heat was focused on a spot 1–2 cm from the tip of the tail, and the time until the mouse flicked its tail (latency) was recorded. Beam intensity was adjusted to give a tail-flick latency of 3.5–4.5 s in control animals. The animals were restrained during trials by means of a plexiglass cylinder 4 cm in diameter and 14 cm long.

The tail-skin temperature was measured on the ventral surface, about 35 mm proximal to the spot where the beam was focused, by means of a copper-constantan thermocouple probe (0.2 mm copper-constantan wire, the junction measuring 0.4 × 0.8 mm).

Both the thermocouple and the tail-flick apparatus were connected via a Biodata Microlink III interface unit to an IBM Personal Computer programmed to record the tail temperature and the tail-flick latency simultaneously. The beam duration was controlled manually from the computer keyboard. The tail-skin temperature was recorded at the moment when the tail flick occurred. This modification of the tail-flick test has been described in detail previously (20).

Hot-plate test. In the hot-plate test (21), an IITC Inc. model 35-D Analgesiameter was set to give a plate temperature of 55 ± 0.5°C. The animals were placed on the hot plate confined by a lidded perspex box with a compartment measuring 13.8 × 13.8 cm, and the latency to the first hind-paw lick was recorded. If no hind-paw lick occurred, the test was terminated after 30 s. The animals were preadapted to the test apparatus by putting each animal in the perspex box on the cold plate for 1–2 min the day before testing.

Testing Procedure

Dose-response studies of morphine, fentanyl, and buprenorphine in the two nociceptive tests were performed initially. Then the effect of diazepam on the opiate dose-response curves in the hot-plate test was studied. For the other interaction studies, submaximal doses of the opiates were chosen, i.e., doses that increased the response latency to about twice of that of saline-treated controls. These doses of opiates were combined with benzodiazepines in the rest of the study. Morphine induced a similar effect in both tests, fentanyl and buprenorphine, however, had a larger effect in the tail-flick test. Lower doses of these drugs were therefore used in this test.

Statistical Analyses

Fisher's exact test was used to analyze the rotarod data. The tail-flick and tail-temperature data were analyzed by analysis of covariance (ANCOVA), and the hot-plate data were analyzed by analysis of variance (ANOVA). Student's *t*-test was used subsequent to ANOVA to compare specific means (22). Statistical significance was accepted at the 5% level ($P < 0.05$).

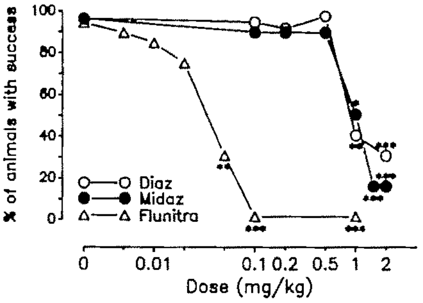

Figure 1. Rotarod performance in mice given diazepam, midazolam, or flunitrazepam. Results are expressed as the percentage of animals that are able to stay on the rod for 45 s. The animals were tested 30 min after drug injection, $n = 10–15$ for each dose level. Statistically significant differences compared to controls are indicated by $^{*}P < 0.02$, $^{**}P < 0.01$, and $^{***}P < 0.001$ (Fischer's exact test).

Table 1. Statistical Evaluation (ANOVA) of the Effect of Diazepam on Opiate Antinociception in the Hot-Plate Test

Opiate	Diazepam dose (mg/kg)	df	F-value	P-value
Morphine	0.2	1, 54	0.48	>0.4
	0.5	1, 56	8.26	<0.01
	1.0	1, 56	9.49	<0.005
Fentanyl	0.2	1, 34	2.48	>0.1
	0.5	1, 34	5.85	<0.05
	1.0	1, 35	5.58	<0.05
Buprenorphine	0.2	1, 53	4.81	<0.05
	0.5	1, 51	8.44	<0.01
	1.0	1, 52	5.45	<0.05

Results

Effect of Benzodiazepines on Sensorimotor Performance

All three benzodiazepines induced a dose-dependent sensorimotor impairment on the rotarod, but flunitrazepam was about 20 times more potent than midazolam and diazepam (Figure 1). Thus, flunitrazepam (50 μg/kg or higher) induced a statistically significant impairment (50 μg/kg: $P < 0.01$, Fisher's exact test). For the other two drugs, a significant effect was observed with doses of 1 mg/kg or higher (1 mg/kg midazolam: $P < 0.02$; 1 mg/kg diazepam: $P < 0.01$).

Effect of Benzodiazepines on Nociception

In the hot-plate test, diazepam and midazolam in doses of up to 1 mg/kg, and flunitrazepam in doses of up to 20 μg/kg, did not induce any significant effects. Higher doses of the drugs, however, significantly increased the response latencies (Student's *t*-test subsequent to ANOVA, data not shown). In the tail-flick test, a significant covariance between tail-skin temperature and tail-flick latency was observed, but even when the change in tail-skin temperature was taken into consideration, no significant effects on the tail-flick latency could be detected (diazepam: $F_{3,19} = 1.65$, $P > 0.2$; midazolam: $F_{3,27} = 0.69$, $P > 0.5$; flunitrazepam: $F_{6,42} = 0.49$, $P > 0.8$, ANCOVA, data not shown).

Effect of Diazepam on Opiate Antinociception

Hot-plate test. Diazepam (0.2–1 mg/kg) was combined with morphine (2–5 mg/kg), fentanyl (20–50 μg/kg), or buprenorphine (75–150 μg/kg). The dose-response curves in saline-treated animals were compared with the dose-response curves in animals given different doses of diazepam. To evaluate the effects of diazepam, the response latencies had to be transformed to relative values because the mean control responses differed somewhat between individual experiments. Statistical evaluation (ANOVA) was then performed on the changes in response latencies.

Diazepam (0.5 and 1 mg/kg) significantly shifted the dose-response curves for all three opiates to the right. The same tendency could also be observed after 0.2 mg/kg diazepam, but only the effect on buprenorphine antinociception reached statistical significance. The statistical evaluation of the data is shown in Table 1, and the effects of 0.2 and 0.5 mg/kg diazepam are shown in Figure 2. The data for the 1-mg/kg dose of diazepam were almost identical to the data for the 0.5-mg/kg dose and are therefore not shown. No effect of diazepam was observed with the highest fentanyl dose (Figure 2B), indicating that the effect of diazepam could be counteracted by increasing the opiate dose, thus resembling competitive antagonism.

Tail-flick test. Diazepam (0.5–2 mg/kg) was combined with either morphine (3 mg/kg), fentanyl (10 μg/kg), or buprenorphine (30 μg/kg). Diazepam dose-dependently antagonized the antinociceptive effect of all three opiates (Figures 3A, 3B, and 3C). Statistical evaluation of the data using two-way ANCOVA (diazepam × opiate, covariate: tail-skin temperature) indicated a highly significant effect of diazepam (morphine-treated animals: $F_{3,55} = 11.11$, $P < 0.001$; fentanyl-treated animals: $F_{3,57} = 6.93$, $P < 0.001$; buprenorphine-treated animals: $F_{2,40} = 5.81$, $P < 0.01$) and a significant interaction between diazepam and all three opiates (morphine × diazepam: $F_{3,55} = 5.60$,

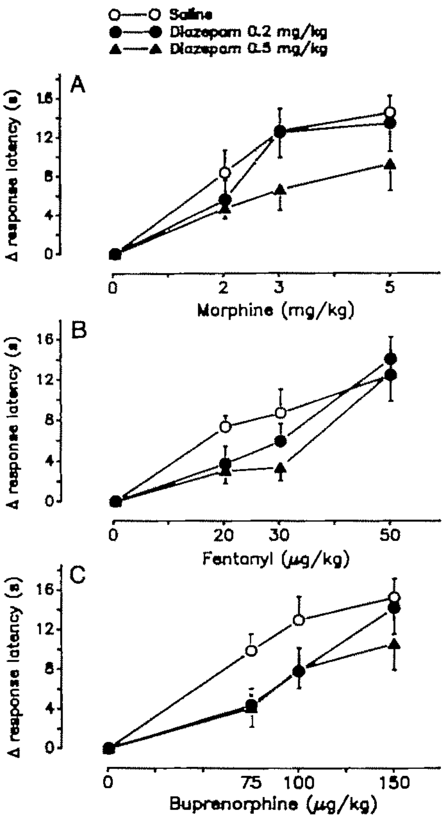

Figure 2. The effect of 0.2 and 0.5 mg/kg diazepam or saline on the dose-response curves of (A) morphine, (B) fentanyl, and (C) buprenorphine in the hot-plate test. Results are given as changes in response latency compared to control animals given saline injections only. Mean ± SEM, n = 9–11 for each data point.

$P < 0.005$; fentanyl × diazepam: $F_{3,57} = 5.10$, $P < 0.001$; buprenorphine × diazepam: $F_{2,40} = 3.94$, $P < 0.05$).

Effect of Midazolam on Opiate Antinociception

Hot-plate test. Midazolam (0.2–1 mg/kg) was combined with either morphine (3 mg/kg), fentanyl (30 μg/kg), or buprenorphine (100 μg/kg) (Figure 4). Two-way ANOVA (midazolam × opiate) showed a dose-dependent effect of midazolam on the antinociceptive effect of all three opiates (morphine-treated animals: $F_{3,106} = 3.80$, $P < 0.02$; fentanyl-treated animals: $F_{2,80} = 3.46$, $P < 0.05$; buprenorphine-treated animals: $F_{3,114} = 3.44$, $P < 0.02$) and a significant interaction between the midazolam effect and the opiate effects: (morphine × midazolam: $F_{3,106} = 3.60$, $P < 0.02$; fentanyl × midazolam: $F_{2,82} = 3.05$, $P < 0.05$; buprenorphine × midazolam: $F_{3,114} = 2.91$, $P < 0.05$).

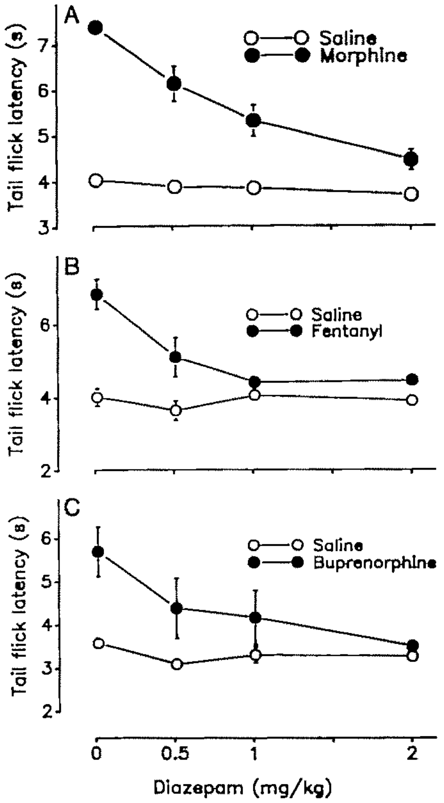

Figure 3. The effect of 0.5–2 mg/kg diazepam on the tail-flick latency in animals given saline or (A) 3 mg/kg morphine, (B) 10 μg/kg fentanyl, or (C) 30 μg/kg buprenorphine. Mean ± SEM, n = 8–12 for each data point.

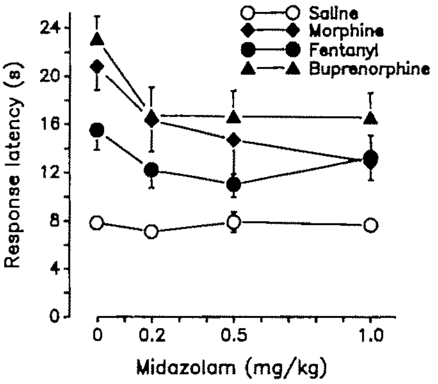

Figure 4. The effect of 0.2–1 mg/kg midazolam on the response latencies in the hot-plate test in animals given 3 mg/kg morphine, 30 μg/kg fentanyl, 100 μg/kg buprenorphine, or saline. Mean ± SEM, n = 8–11 for each data point.

Tail-flick test. Midazolam (0.5–2 mg/kg) was combined with morphine (3 mg/kg), fentanyl (10 μg/kg), or buprenorphine (30 μg/kg). Midazolam dose-dependently antagonized the effect of all three opiates (Figure 5). Statistical evaluation of the data using two-way ANCOVA (midazolam × opiate, covariate: tail-skin temperature) indicated a significant effect of midazolam (morphine-treated animals: $F_{3,58} = 3.87$, $P < 0.02$; fentanyl-treated animals: $F_{3,53} = 15.99$, $P <$

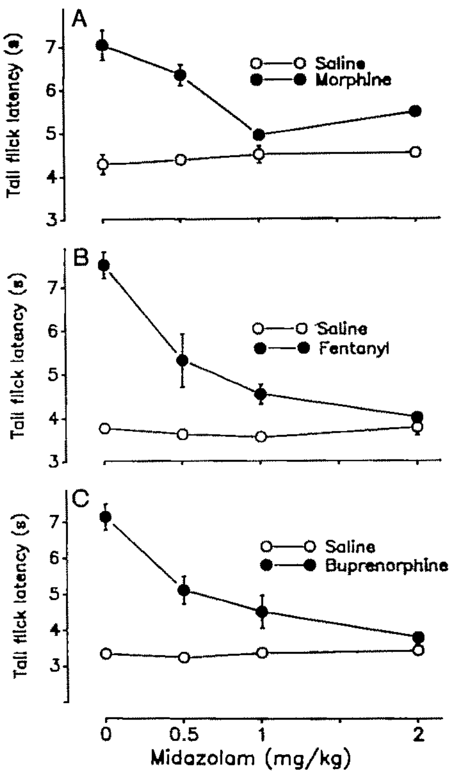

Figure 5. The effect of 0.5–2 mg/kg midazolam on the tail-flick latency in animals given saline or (A) 3 mg/kg morphine, (B) 10 μg/kg fentanyl, or (C) 30 μg/kg buprenorphine. Mean ± SEM, n = 8–12 for each data point.

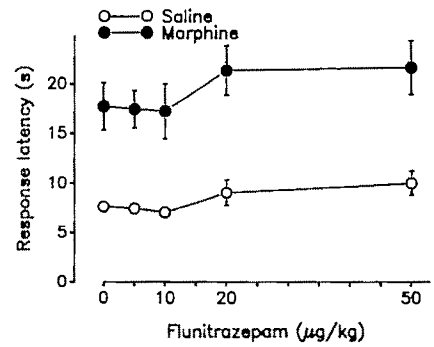

Figure 6. The effect of 10–50 μg/kg flunitrazepam on the response latencies in the hot-plate test in animals given 3 mg/kg morphine or saline. Mean ± SEM, n = 7–9 for each data point.

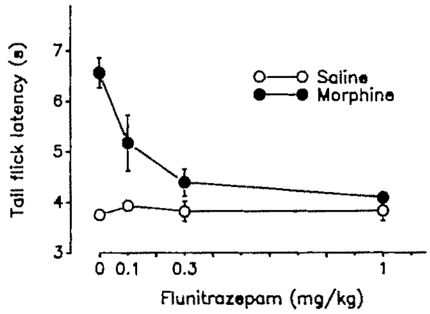

Figure 7. The effect of flunitrazepam on the tail-flick latency in animals given 3 mg/kg morphine or saline. Mean ± SEM, n = 7–10 for each data point.

0.001; buprenorphine-treated animals: $F_{3,55} = 10.67$, $P < 0.001$) and a significant interaction between midazolam and all three opiates (morphine × midazolam: $F_{3,58} = 8.03$, $P < 0.001$; fentanyl × midazolam: $F_{3,56} = 14.19$, $P < 0.001$; buprenorphine × midazolam: $F_{3,55} = 12.07$, $P < 0.001$).

Effect of Flunitrazepam on Opiate Antinociception

Hot-plate test. Flunitrazepam (5–50 μg/kg) did not induce any significant effect in combination with morphine (3 mg/kg) ($F_{4,67} = 1.42$, $P > 0.2$, ANOVA; Figure 6). The highest doses of flunitrazepam used tended to increase the response latencies both in saline- and morphine-treated animals. Using higher doses of flunitrazepam, the test could not be performed because of marked sedation.

Tail-flick test. Flunitrazepam in doses of up to 50 μg/kg did not influence the antinociceptive effect of 3 mg/kg morphine. However, when the dose of flunitrazepam was further increased, antagonism similar to that seen with diazepam and midazolam could be observed. Thus, 0.1–1 mg/kg flunitrazepam significantly antagonized the antinociceptive effect of morphine (effect of flunitrazepam: $F_{3,64} = 2.79$, $P < 0.05$; morphine × flunitrazepam: $F_{3,64} = 6.07$, $P < 0.001$, ANCOVA, Figure 7).

Discussion

This study shows that the antinociceptive effects of different opiates may be antagonized by different benzodiazepines. In the hot-plate test, diazepam induced a rightward shift of the dose-response curves for morphine, fentanyl, and buprenorphine in a competitive manner. In the tail-flick test, 0.5–2 mg/kg diazepam dose-dependently attenuated the effect of all three opiates. Midazolam had similar effects on opiate antinociception as diazepam. Flunitrazepam in doses of up to 50 μg/kg did not significantly influence the effect of morphine in the hot-plate test, but higher doses antagonized the effect of morphine in the tail-flick test.

The rotarod data indicated that all three benzodiazepines were able to induce sensorimotor impairment. Flunitrazepam was about 20 times more potent than the other two drugs in this respect and is also known to be a potent hypnotic (23). Very low doses of flunitrazepam, therefore, had to be chosen to avoid sedation. These low doses, however, had no effect on morphine antinociception. As the tail-flick reflex also is present in sedated or lightly anesthetized animals (24), we examined the effect of higher flunitrazepam doses using the tail-flick test, and the same antagonism as seen with the other two benzodiazepines could be demonstrated using doses of 0.1–1 mg/kg flunitrazepam.

It has been demonstrated that the tail-flick latency is greatly influenced by the tail-skin temperature, and, therefore, the tail-skin temperature and the tail-flick latency were measured simultaneously (20). However, the effects of benzodiazepines in the present study could not be explained by alteration of tail-skin temperature.

Diazepam (2 mg/kg), midazolam (2 mg/kg), and flunitrazepam (50 μg/kg) increased the response latencies in the hot-plate test. These benzodiazepine doses also induced significant impairment of the performance on the rotarod. The apparent antinociceptive effect observed with these doses may therefore be due to a reduced ability to perform the motor response. An impaired motor response could also explain why no additional attenuation of the opiate effect was observed when the dose of midazolam and diazepam was increased from 0.5 to 1 mg/kg.

The sedative and muscle-relaxing effects of benzodiazepines may complicate the interpretation of tests based on motor responses (18). These effects may mask an antagonism between benzodiazepines and opiates, and may partly explain why different conclusions have been reached in different studies (8,9,11). Different nociceptive tests may also differ in their sensitivity to muscle-relaxing effects, and thus different results may be obtained in different tests when interaction between benzodiazepines and opiates are studied (17). Different species may also respond differently to muscle relaxation (25). In anesthetic practice, where opiates and benzodiazepines are usually combined, it may be difficult to evaluate a possible interaction because of sedation. The benzodiazepines also induce amnesia, an effect that may further complicate the evaluation (1). In spite of these difficulties, antagonism between diazepam and morphine also has been reported in humans (26).

Flunitrazepam induced sensorimotor impairment after a dose that was less than one-fourth of that needed to induce any effects on morphine antinociception; midazolam and diazepam showed opiate antagonism after doses that did not affect sensorimotor performance. Opiate antagonism and sensorimotor impairment may therefore involve separate mechanisms. However, as both effects are blocked by benzodiazepine receptor antagonists (9,16,27), benzodiazepine receptors seem to be involved in both mechanisms. The different benzodiazepine effects may therefore be mediated by separate receptor subtypes (10,27–29). Uneven distribution of benzodiazepine receptor subtypes in different parts of the central nervous system could also explain the test-dependent effects of opiate and benzodiazepine interactions described (8,17). It has been demonstrated that benzodiazepines injected into the periaqueductal gray matter may antagonize morphine antinociception (7), suggesting that these brainstem structures may be involved in these interactions. Further investigations have to be performed to clarify the mechanisms of these interactions.

In conclusion, midazolam and diazepam attenuated the antinociceptive effect of three different opiates in the hot-plate test and the tail-flick test in mice. The effect of flunitrazepam could only be demonstrated in the tail-flick test due to a marked sedative effect in the hot-plate test. As the antagonism did not correlate well with the sedative or muscle-relaxing properties of the benzodiazepines, separate mechanisms for these properties may exist. It is hypothesized that these different effects may be linked to separate subtypes of benzodiazepine receptors, but could also involve other mechanisms.

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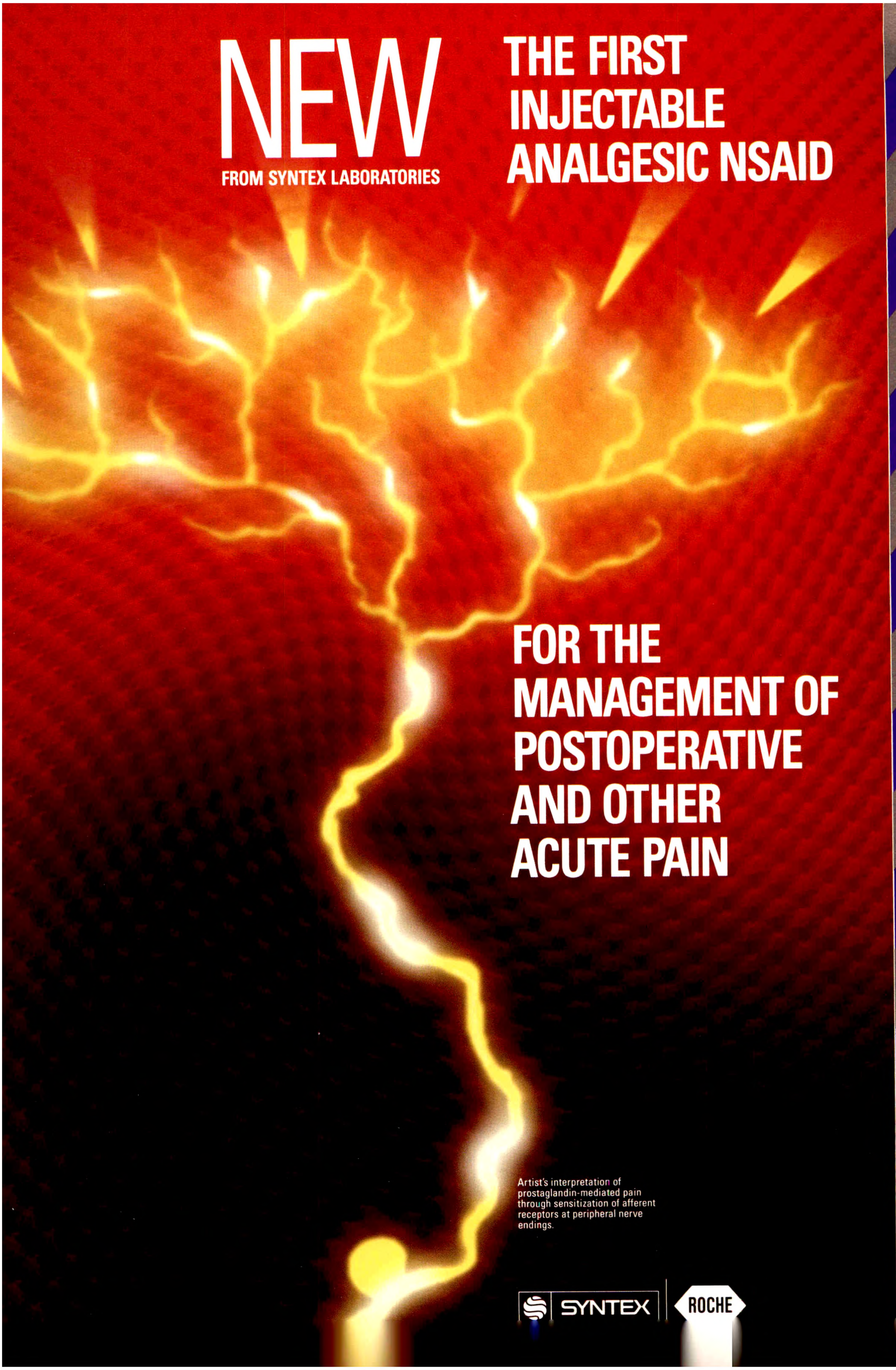
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FROM SYNTEX LABORATORIES
THE FIRST INJECTABLE ANALGESIC NSAID
FOR THE MANAGEMENT OF POSTOPERATIVE AND OTHER ACUTE PAIN
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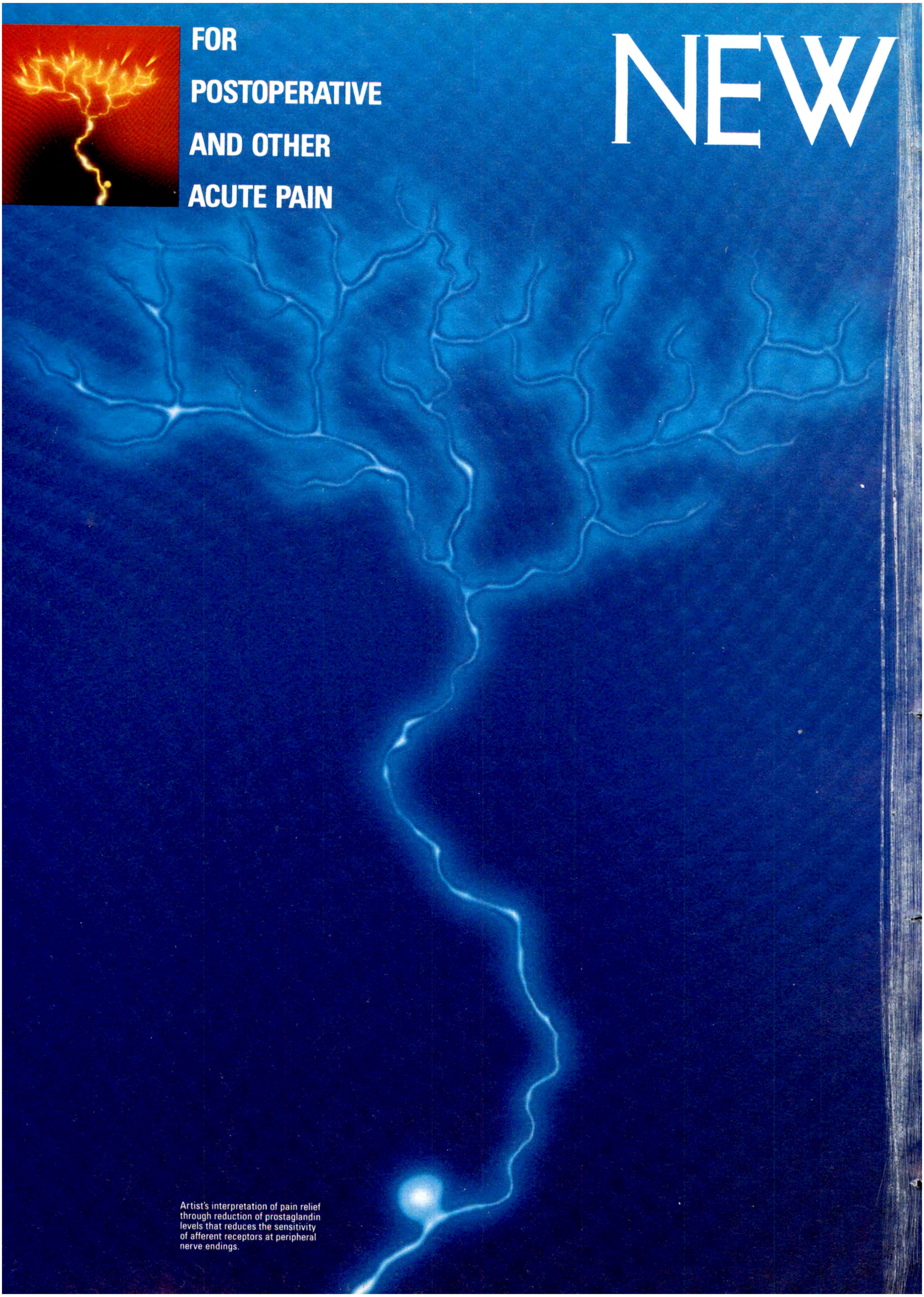
Artist's interpretation of prostaglandin-mediated pain through sensitization of afferent receptors at peripheral nerve endings.



Artist's interpretation of pain relief through reduction of prostaglandin levels that reduces the sensitivity of afferent receptors at peripheral nerve endings.

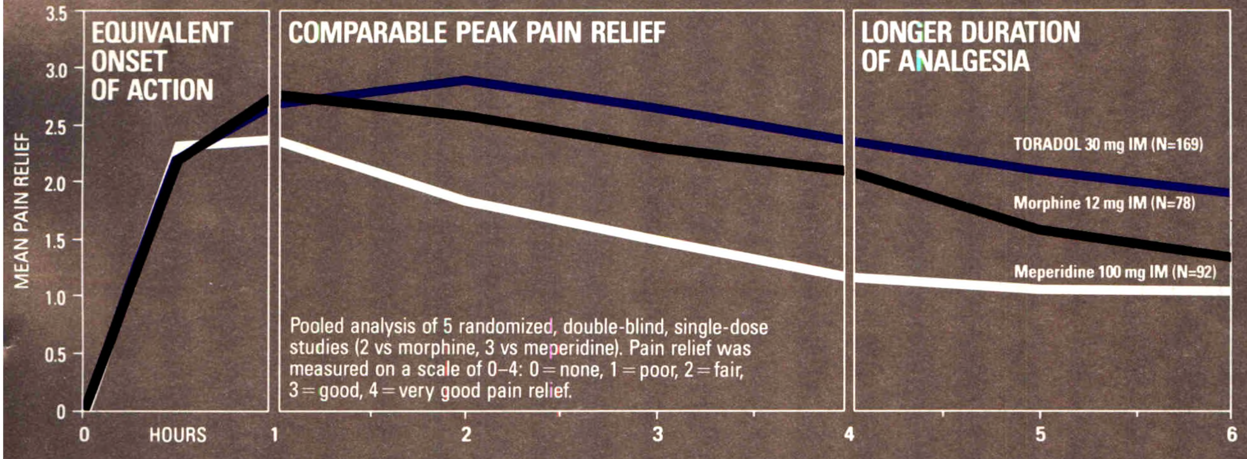
TORADOL® IM INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

The first peripherally acting analgesic with efficacy comparable to morphine 12 mg and meperidine 100 mg

Analgesic efficacy of TORADOL IM administered 24–72 hours postsurgery[1]



Pooled analysis of 5 randomized, double-blind, single-dose studies (2 vs morphine, 3 vs meperidine). Pain relief was measured on a scale of 0–4: 0 = none, 1 = poor, 2 = fair, 3 = good, 4 = very good pain relief.

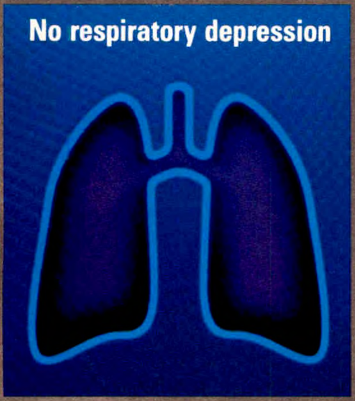
Documented efficacy following a broad range of surgical procedures:

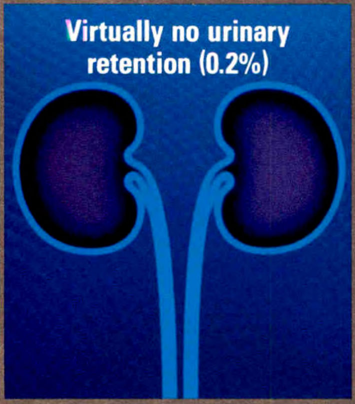
General, orthopaedic, gynecologic (not for obstetric use)

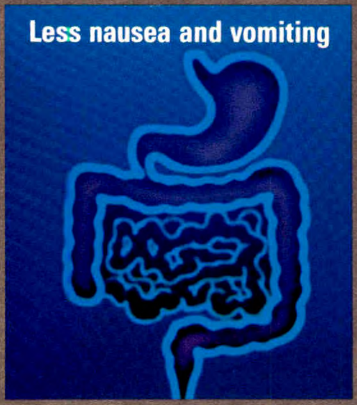
*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings" and "Precautions" sections of prescribing information.

[1] Data on file, Syntex Laboratories, Inc., Document #90037-1.

Please see brief summary of prescribing information on last page of this advertisement.



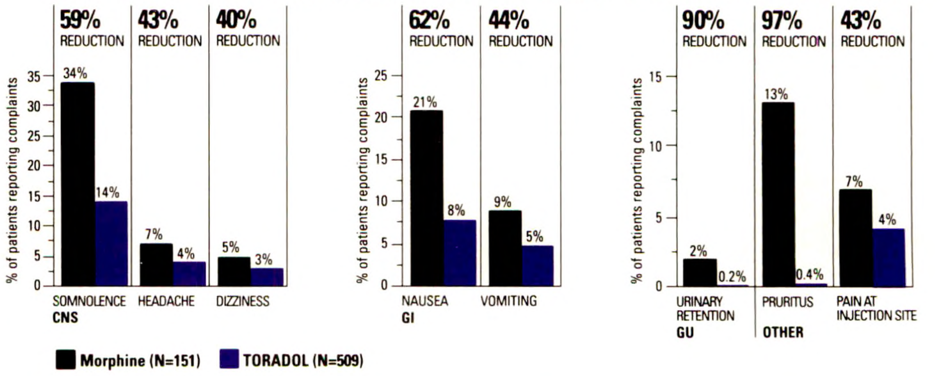




START RECUPERATION WITHOUT NARCOTIC SIDE EFFECTS[1]*

- 62% less nausea and 44% less vomiting
- 48% fewer CNS side effects
- No respiratory depression
- No hypotension
- 1-day earlier resumption of normal bowel function following major abdominal surgery
- No difference in clinically significant postoperative bleeding with TORADOL IM (0.4%) as compared to opiates (0.2%)

Comparison of most frequently reported side effects in 2 multi-dose studies (TORADOL IM vs morphine)**



Adverse reactions rates from short-term use of NSAIDs are generally from 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL IM.

**FOR
POSTOPERATIVE
AND OTHER
ACUTE PAIN**

NEW

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*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings," "Precautions," and "Adverse Reactions" sections of prescribing information.

**Most frequently reported side effects in major body systems with the exception of the cardiovascular system. 2% of patients treated with Toradol reported vasodilation as compared to 1% of patients treated with morphine.

1. Documented in 2 randomized, double-blind, multi-dose studies in which 509 patients received ketorolac 30 mg and 151 patients received morphine 10 mg or morphine 12 mg. Bowel function was evaluated in a subset of 47 patients undergoing gastric bypass surgery. Data on file, Syntex Laboratories, Inc., Document #90037-2.
2. Data on file, Syntex Laboratories, Inc., Document #90037-3.

Please see brief summary of prescribing information on last page of this advertisement.

Analgesic therapy well suited for postoperative use

TORADOL IM is not an opiate

- Does not act on opiate receptor sites
- No potential for abuse
- No special restrictions or controls required

May be an appropriate alternative to narcotics for:

- Patients with narcotic allergy or intolerance
- Patients with a history of, or potential for, drug abuse or dependence

Special advantages may facilitate postoperative recuperation

- Patients with COPD or the obese–no negative effects on pulmonary function
- Ambulatory surgery patients–less CNS impairment (e.g., 59% less somnolence and 40% less dizziness)

Optimize analgesia on the day of surgery

- On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing
- On average, only one supplemental dose of narcotics may be required[2]

TORADOL® IM
INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

FOR
POSTOPERATIVE
AND OTHER
ACUTE PAIN

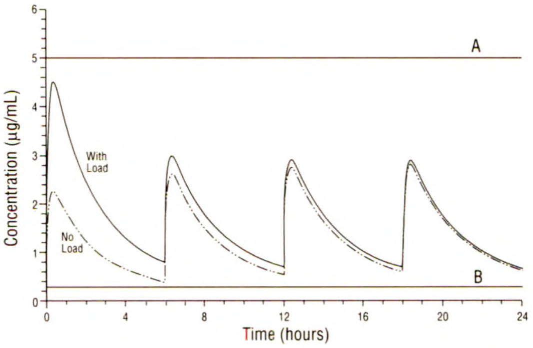
NEW TORADOL® IM INJECTION (KETOROLAC TROMETHAMINE) 15, 30, 60 MG

OPTIMIZE ANALGESIC THERAPY FOR THE POSTOPERATIVE PATIENT

PROPER DOSAGE POSTOPERATIVELY

For maximum analgesia:

- Give patients prompt pain relief: start with loading dose of 60 mg IM
- Follow with maintenance dose of 30 mg IM Q6h to control pain
- The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter*



Simulated incremental plasma concentrations after 2 multi-dose regimens: (1) TORADOL IM 30 mg Q6h (no load); (2) TORADOL IM 60 mg LOADING DOSE followed by 30 mg Q6h

A = Plasma concentration above which side effects are more frequent

B = Estimated concentration required to obtain 50% decreases in pain intensity scores in dental surgery pain

Achieve optimal peak and trough plasma levels by starting with a loading dose (e.g., 60 mg), while maintaining plasma levels within the recommended therapeutic range. Follow with maintenance doses (e.g., 30 mg every 6 hours) to keep plasma levels in the optimal range.

Patient Selection: Use in patients with moderate-to-severe postoperative pain following general, orthopaedic, or gynecologic surgery (not for obstetric use)

Lower doses:

- Recommended for patients under 50 kg (110 pounds), patients over 65 years of age, and patients with reduced renal function
- Start with loading dose of 30 mg IM
- Follow with maintenance dose of 15 mg IM Q6h to control pain

On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing (not compatible in same syringe)

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*Dosages above those recommended are not associated with commensurate increases in efficacy.

Please see brief summary of prescribing information on last page of this advertisement.

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1991 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1991 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than **December 14, 1990.** Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1991 Award(s) will be announced at the Annual Scientific Meeting (65th Congress) of the International Anesthesia Research Society to be held at the Marriott Rivercenter, San Antonio, Texas, March 8–12, 1991.

TORADOL® IM (ketorolac tromethamine)

Brief Summary
TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP, and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 μg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 μg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the in vivo mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery. **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. **Pediatric Use:** TORADOL is not recommended for use in children. **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. **Incidence greater than 1%:** Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%-9%. Reactions occurring in less than 3% are unmarked. **Incidence 1% or less:** Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. In vitro, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses >100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration**: TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others.

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An Invaluable Source for Neurologists and Neurosurgeons

Focal Peripheral Neuropathies

John D. Stewart, B.Sc., M.B., B.S., M.R.C.P., F.R.C.P.(C),
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Director EMG Laboratory, The Montreal General Hospital, Montreal, Quebec

Illustrated by **Margo Siminovitch, B.Sc., A.A.M.**, Director of Educational Resources, The Montreal General Hospital, Montreal, Quebec

Focal Peripheral Neuropathies is a comprehensive reference source for all physicians and surgeons who treat patients with acute and chronic peripheral nerve lesions. Neurologists and neurosurgeons, as well as hand and plastic surgeons, orthopedists, rheumatologists, and specialists in physical medicine and rehabilitation will find this well illustrated volume presents clinical and research information directly applicable to practice.

This 421 page, 24 chapter text is devoted to the study of lesions of the individual peripheral nerves, from the spinal nerve roots to the terminal digital branches. The text systematically discusses the causes, symptoms, and differential diagnoses of radiculopathies, plexopathies, and focal neuropathies involving individual peripheral nerve trunks and their more important branches.

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6 The Cervical Plexus and the Nerves of the Neck
7 The Brachial Plexus
8 The Nerves Arising from the Brachial Plexus
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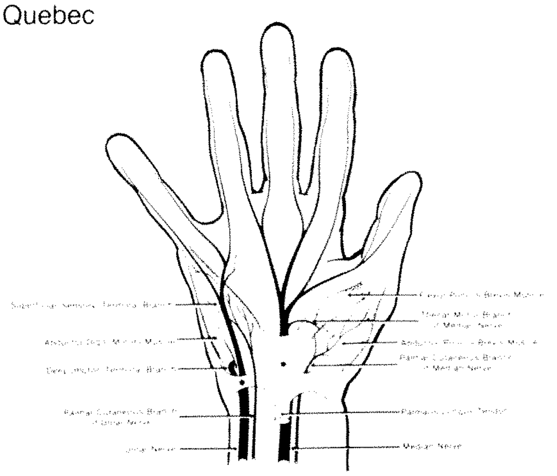
11 The Radial Nerve
12 The Digital Nerves
13 The Cauda Equina, Lumbar and Sacral Nerve Roots, and Spinal Nerves



Superficial Sensory Terminal Branch
Abductor Digiti Minimi Muscle
Deep (Motor) Terminal Branch
Palmar Cutaneous Branch of Ulnar Nerve
Ulnar Nerve
Flexor Pollicis Brevis Muscle
Thenar Motor Branch of Median Nerve
Abductor Pollicis Brevis Muscle
Palmar Cutaneous Branch of Median Nerve
Palmaris Longus Tendon
Median Nerve

FIGURE 12.1 Palmar view of the right wrist and hand, showing the course and branching of the median and ulnar nerves. These nerves first divide into the common digital nerves, which then divide further to become individual proper palmar digital nerves. The transverse carpal ligament and its extension, which forms the roof of Guyon's canal, are marked with asterisks.

14 The Lumbosacral Plexus
15 The Sciatic Nerve, the Gluteal and Pudendal Nerves, and the Posterior Cutaneous Nerve of the Thigh
16 The Common Peroneal Nerve
17 The Tibial, Plantar, Interdigital, and Sural Nerves
18 The Femoral and Saphenous Nerves
19 The Lateral Cutaneous Nerve of the Thigh
20 The Obturator Nerve
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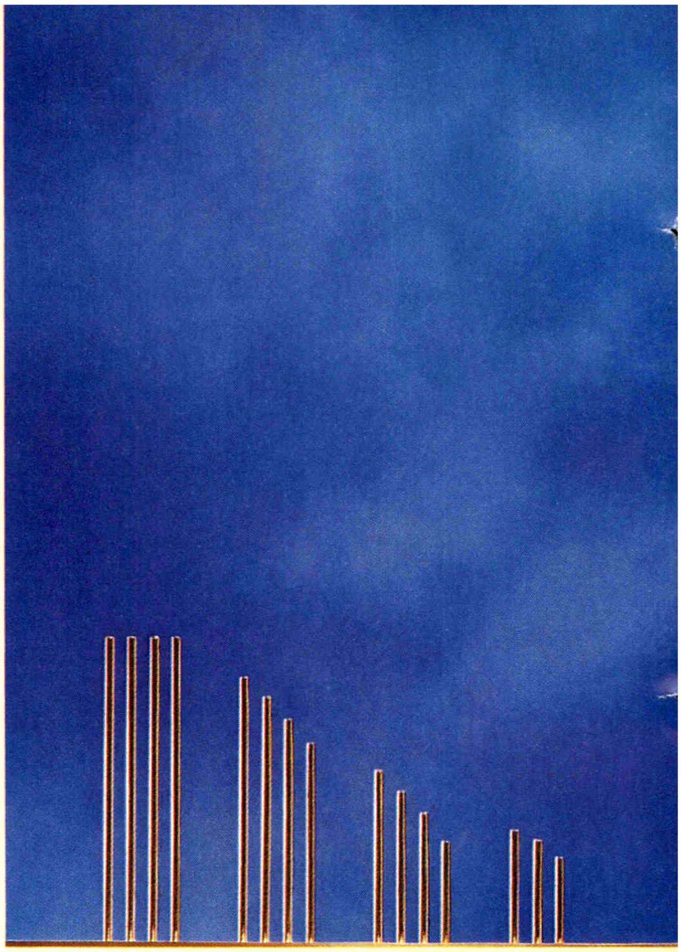

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- Good to excellent intubating conditions, 2.5 to 3 minutes

As with other long-acting non-depolarizing neuromuscular blocking agents, ARDUAN® displays a variability in the clinical duration of its effect.

Mean Change From Baseline in Heart Rate, Systolic and Diastolic Blood Pressure

	ARDUAN® 70 mcg/kg		**Pancuronium** 100 mcg/kg	
	Before	2 Min After	Before	2 Min After
Heart Rate (beats/min)	68.9 ± 13.1	72.9 ± 14.1	72.0 ± 15.3	91.4 ± 17.1*
Systolic Blood Pressure (mm Hg)	110.01 ± 18.7	107.0 ± 16.2	107.4 ± 14.4	117.6 ± 14.3*
Diastolic Blood Pressure (mm Hg)	66.0 ± 13.1	64.4 ± 10.4	61.3 ± 12.3	69.0 ± 14.6

*$P < .05$ different from baseline values.

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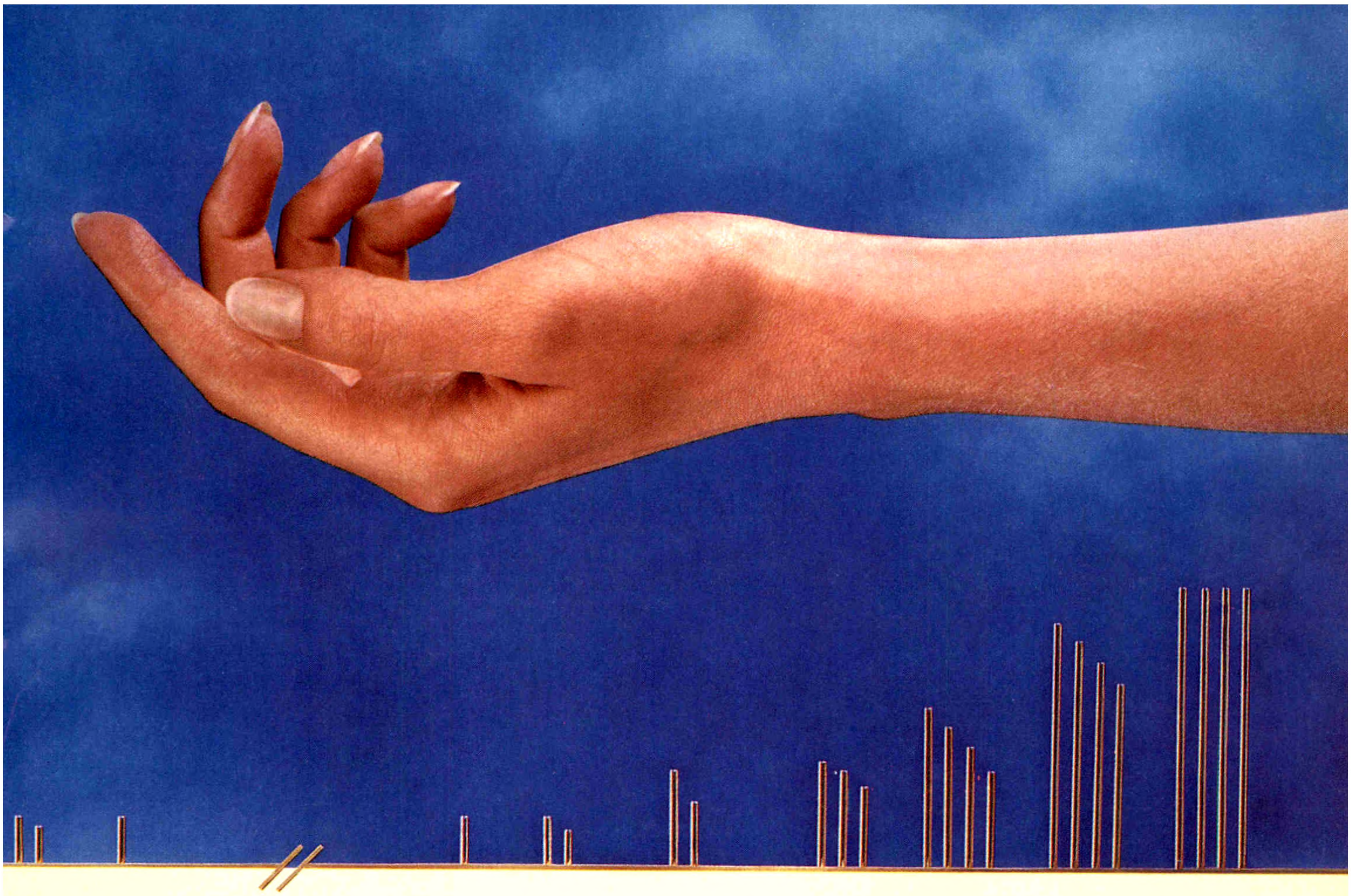
*Recommended only for procedures 90 minutes or longer.

Reference
1. Data on file.



NEW

ARDUAN®

(pipecuronium bromide)
for injection

FOR LONG SURGICAL PROCEDURES

See brief summary of prescribing
information on the following page.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

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NEW

ARDUAN®

(pipecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known.
WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.
PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.
Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.
Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.
Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.
Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.
Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.
Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.
Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.
Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.
Drug/Laboratory Test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.
Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.
Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{95}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.
ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:
Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.
Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.
Musculoskeletal: muscle atrophy, difficult intubation.
Nervous: hypesthesia, CNS depression.
Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.
Skin and Appendages: rash, urticaria.
Urogenital System: anuria.
HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36) 10 mL vials containing 10 mg lyophilized pipecuronium bromide and 10 mL vials containing bacteriostatic water for injection, USP. Boxes of 6 (NDC 0052-0446-37)
Storage: 2°-30°C (36°-86°F). Protect from light.
After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

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ORGANON INC. WEST ORANGE, NEW JERSEY 07052

or by

BEN VENUE LABS., INC. BEDFORD, OHIO 44146
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For complete information contact Mrs. Carolyn Schoenau, Program Coordinator, Anesthesiology Alumni Association of Florida, Inc., Post Office Box 13417, Gainesville, Florida 32604 (Area code 904 392-8959).

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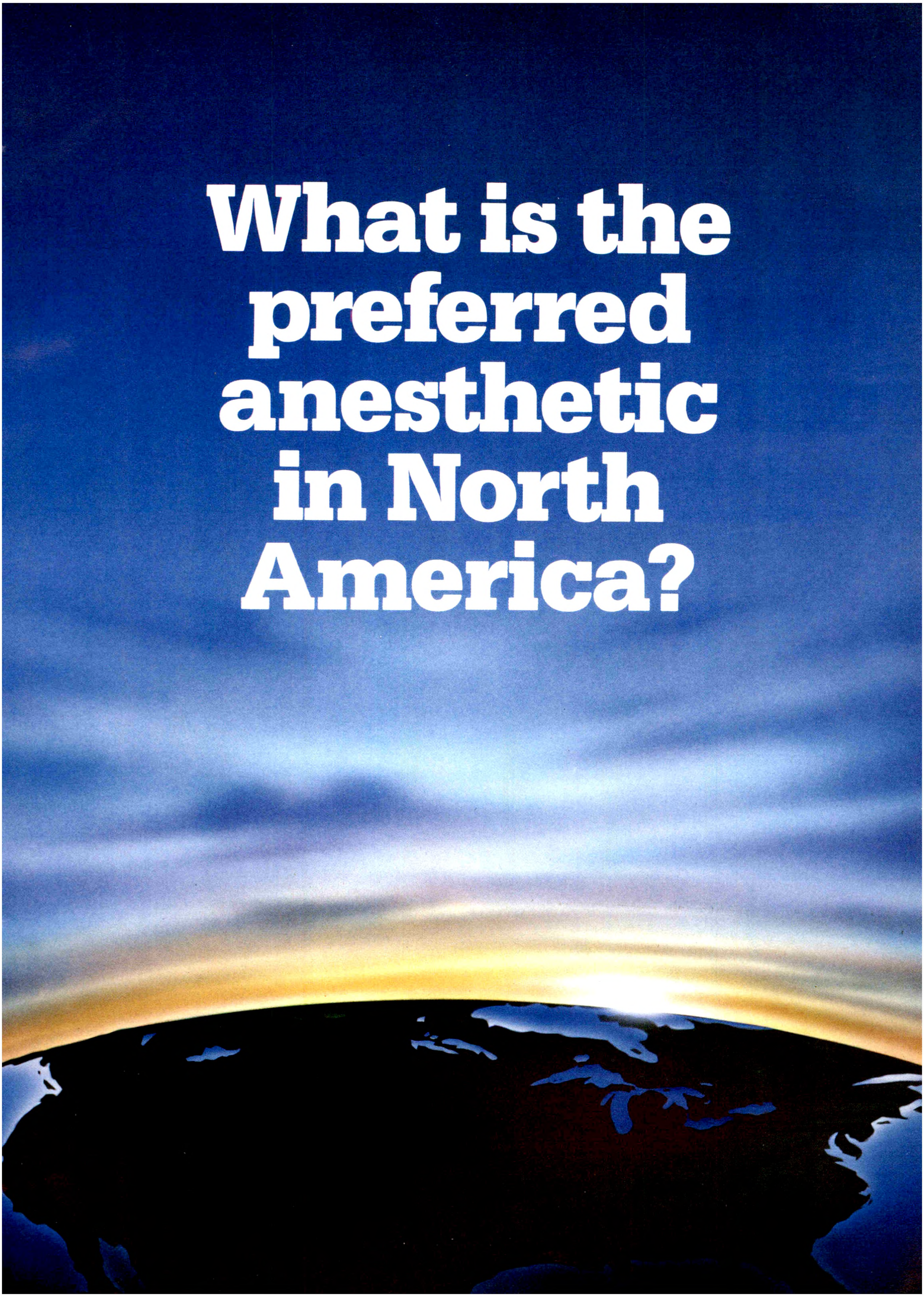
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FORANE®... Complete,

(isoflurane, USP)

Preferred in North America

A Complete Anesthetic

(with or without nitrous oxide)

- Unconsciousness
- Amnesia
- Analgesia
- Surgical muscle relaxation

True "Moment-to-Moment" Control

- Little patient-to-patient variability of dose response
- Low blood/gas solubility, for rapid, precise changes in depth

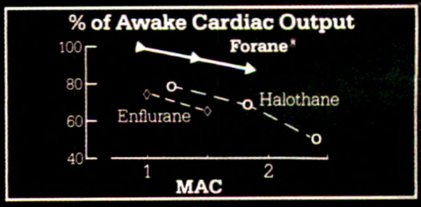
Blood/Gas Solubility

Agent	Blood/gas partition coefficient at 37°C
Forane®	**1.4**
Halothane	2.3
Enflurane	1.9

From Eger EI II. Isoflurane (Forane®), A Compendium and Reference, 2nd ed. Madison, WI, Anaquest, 1985.

Cardiovascular Stability

- Little myocardial depression



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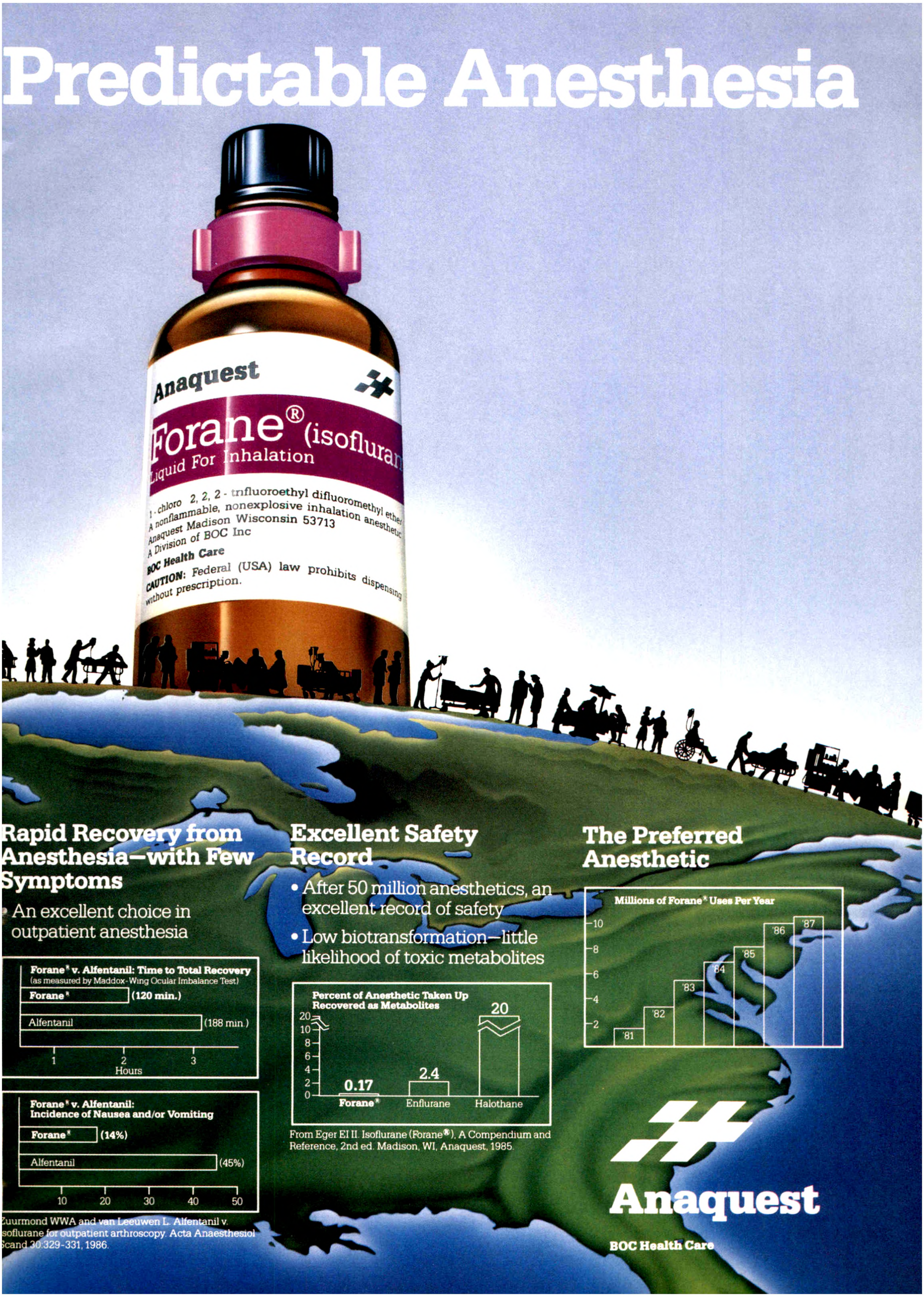
- Notable stability of heart rhythm
- Excellent control of blood pressure
- Often beneficial in geriatric anesthesia



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Forane® (isofluran
Liquid For Inhalation
1 - chloro 2, 2, 2 - trifluoroethyl difluoromethyl ether
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Rapid Recovery from Anesthesia—with Few Symptoms

- An excellent choice in outpatient anesthesia

Forane® v. Alfentanil: Time to Total Recovery
(as measured by Maddox-Wing Ocular Imbalance Test)

Forane® (120 min.)
Alfentanil (188 min.)
1
2
3
Hours

Forane® v. Alfentanil: Incidence of Nausea and/or Vomiting

Forane® (14%)
Alfentanil (45%)
10
20
30
40
50

uurmond WWA and van Leeuwen L. Alfentanil v. soflurane for outpatient arthroscopy. Acta Anaesthesiol cand 30:329-331, 1986.

Excellent Safety Record

- After 50 million anesthetics, an excellent record of safety
- Low biotransformation—little likelihood of toxic metabolites

Percent of Anesthetic Taken Up Recovered as Metabolites

From Eger EI II. Isoflurane (Forane®), A Compendium and Reference, 2nd ed. Madison, WI, Anaquest, 1985.

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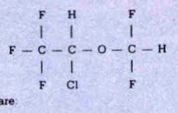
FORANE® (isoflurane, USP)

Preferred in North America

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\mathrm{F-\overset{F}{\underset{F}{C}}-\overset{H}{\underset{Cl}{C}}-O-\overset{F}{\underset{F}{C}}-H}$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \qquad \text{where:} \quad \begin{aligned} A &= 8.056 \\ B &= -1664.58 \\ T &= {}^\circ C + 273.16 \text{ (Kelvin)} \end{aligned}$$

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O.

See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;

b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\, P_V\, F_V}{F_T\,(P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature 15° - 30°C (59° - 86°F). Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

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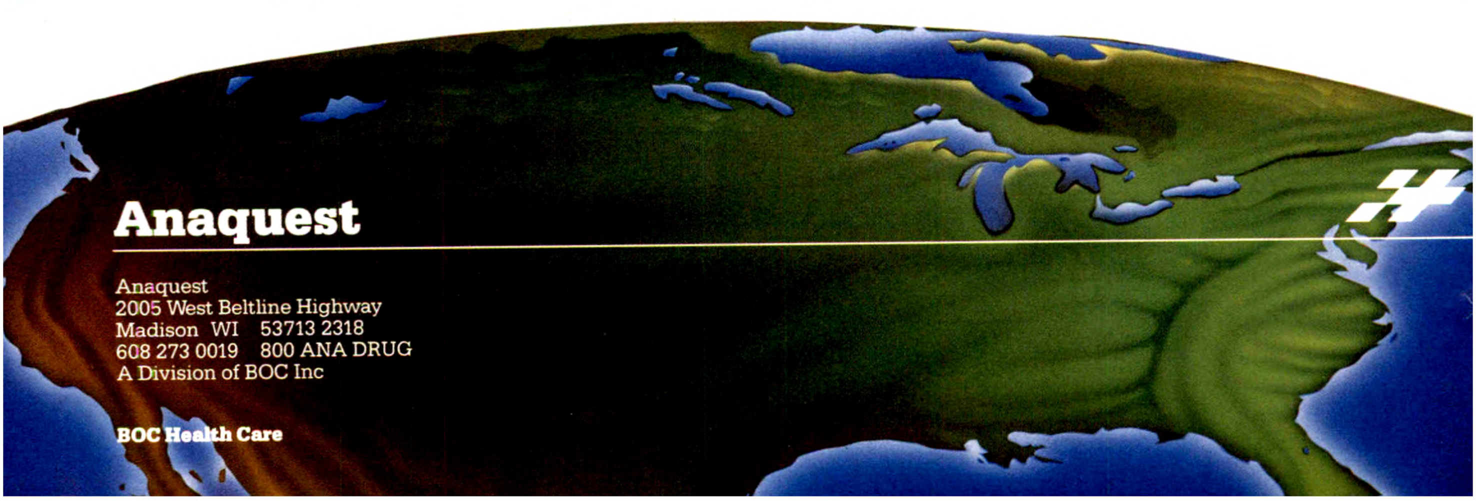

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Hepatocellular Integrity in Swine After Prolonged Desflurane (I-653) and Isoflurane Anesthesia: Evaluation of Plasma Alanine Aminotransferase Activity

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HOLMES MA, WEISKOPF RB, EGER EI II, JOHNSON BH, RAMPIL IJ. Hepatocellular integrity in swine after prolonged desflurane (I-653) and isoflurane anesthesia: evaluation of plasma alanine aminotransferase activity. Anesth Analg 1990;71:249–53.

Desflurane, formerly known as I-653 (CF_2H-O-CFH-CF_3), is a new inhalation anesthetic derived by fluorine substitution for the α-ethyl chlorine of isoflurane (CF_2H-O-CClH-CF_3). The lower solubility and increased stability of desflurane provided by the C–F bond lessen biotransformation to potentially hepatotoxic metabolites. Repeated administration of desflurane to rats, with or without induced hepatic enzymes, does not result in evidence of hepatic injury. In the recent study we extended the tests for liver cell injury to another species, the pig. Our test included prolonged exposure to desflurane or isoflurane, both in the absence and presence of commonly used adjuvants. We measured plasma alanine aminotransferase activity in eight young female swine anesthetized in random order with desflurane (0.8–1.6 MAC) and isoflurane (0.7–1.4 MAC), for a total dose of about 5.5 MAC-hours of each anesthetic, 3–8 days apart. Plasma alanine aminotransferase activities remained in the normal range, and were not significantly greater over baseline values in samples drawn immediately after, 4 h after, or 3–8 days after (mean ± SD, 6.1 ± 2.1) the administration of either anesthetic was discontinued after the first study with either desflurane or isoflurane. Five additional pigs were given a mean total dose of 9.7 MAC-hours of desflurane or isoflurane in conjunction with succinylcholine, N_2O, fentanyl, naloxone, atracurium, thiopental, edrophonium, and atropine. No changes in plasma alanine aminotransferase activity were detected in blood samples drawn at termination of the anesthesia, 24 h later, and 4–7 days later (mean ± SD, 5.8 ± 1.3). Thus, after exposure to desflurane or isoflurane, with or without the use of several anesthetic adjuvants, there was no evidence of hepatic injury.

Key Words: ANESTHETICS, VOLATILE—desflurane, isoflurane. TOXICITY, DESFLURANE, ISOFLURANE. LIVER, HEPATOTOXICITY. ENZYMES, ALANINE AMINOTRANSFERASE.

The relatively low solubility (1) of the experimental inhalation anesthetic desflurane results in rapid onset of and recovery from anesthesia (2). The rapid elimination of desflurane limits its exposure to metabolic enzymes that may convert it to hepatotoxic or nephrotoxic by-products. Recent studies of fluoride ion levels in the blood after 2 h of desflurane exposure in enzyme-induced rats (3) and in eight of the same swine used in the present study (4) suggest that desflurane undergoes little or no metabolism, indicating minimal biodegradation. Repetitive exposure of rats to desflurane, and exposure of hypoxic, hepatic-enzyme-induced rats to desflurane failed to produce morphologic signs of hepatic injury (5,6).

However, biochemical evidence of liver cell death or disturbances in cell permeability evidenced by elevated plasma levels of alanine aminotransferase (ALT) activity often may be found before histologic changes are detectable (7). Furthermore, absence of toxicity in a single species does not provide adequate assurance of safety. To further test the potential of desflurane to cause hepatic injury, we measured plasma ALT activity in eight young female swine before and after prolonged anesthesia (mean, 5.5 MAC-hours) with desflurane at concentrations ranging from 0.8 to 1.6 MAC and with isoflurane from 0.7

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to 1.4 MAC. We also measured plasma ALT levels in another group of five swine successively given succinylcholine, nitrous oxide (N_2O), fentanyl, naloxone, atracurium, thiopental, edrophonium, and atropine during 7–9 h of 1.2 MAC desflurane or isoflurane anesthesia.

Methods

The protocol was approved by the Committee on Animal Research of the University of California at San Francisco.

Animal Preparation and Anesthetic Exposure

Two groups (group 1, $n = 8$; group 2, $n = 5$) of female swine (Landrace crossbreed, Pork Power, Turlock, Calif.), about 10 wk old and weighing 15–20 kg, were prepared under halothane, isoflurane, and desflurane anesthesia with chronically indwelling aortic and pulmonary arterial cannulae (8). Cefazolin was given intravenously, 500 mg/day, for 3 days after surgery.

Aortic blood samples were drawn from conscious swine held in a padded sling (Charles River Labs, Wilmington, Mass.) 3–14 days (mean ± SD, 6.6 ± 2.8) postoperatively. Anesthesia then was induced with desflurane or isoflurane in O_2 via a mask, and succinylcholine chloride, 2 mg/kg IV, was given through the right atrial lumen of the pulmonary artery catheter to facilitate tracheal intubation. Each swine was anesthetized with desflurane or isoflurane in O_2 in random order, with 3–8 days (mean ± SD, 6.0 ± 1.8) separating the two anesthetic administrations.

Group 1 swine received 5.5 ± 1.0 MAC-hours of desflurane and 5.4 ± 0.3 MAC-hours of isoflurane at concentrations varied in random order of 0.8, 1.2, and 1.6 MAC for desflurane and 0.7, 1.05, and 1.4 MAC for isoflurane (9). During the last 1–2 h of anesthesia, epinephrine was infused at increasing rates (from 0.2 to 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to define in the threshold for induction of arrhythmias (10).

Group 2 swine received 9.7 ± 0.73 MAC-hours of each anesthetic during which they were successively given succinylcholine (1 and 2 mg/kg), N_2O (60%), fentanyl (50-μg/kg bolus and 67-$\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion or 100-μg/kg bolus and 134-$\mu g \cdot kg^{-1} \cdot h^{-1}$ infusion), naloxone (0.1 mg/kg), atracurium (0.6 mg/kg), thiopental (2.5 and 5.0 mg/kg), and a mixture of edrophonium (0.5 mg/kg) and atropine (0.005 mg/kg) via the right atrial injection port. Desflurane and isoflurane concentrations were maintained at 1.2 MAC throughout except that the administration of both anesthetics was discontinued for about 30 min while N_2O was washed in and washed out.

All surgery and experiments were conducted using a closed-circle anesthesia circuit with a soda lime absorber. Circulating heated water pads were used to maintain body temperature at ±0.5C° of the value measured while the pig was conscious. Animals were ventilated with a tidal volume of about 20 mL/kg, with frequency adjusted to maintain normocarbia. FIO_2 was maintained at 0.6–0.7. End-tidal concentrations of desflurane were monitored with a Beckman LB-2 infrared analyzer, and end-tidal isoflurane concentrations were determined with a Puritan-Bennett Anesthetic Agent Monitor 222. Both instruments were calibrated with secondary (tank) standards. In measuring desflurane, alinearity of the LB-2 infrared analyzer was accounted for; the Puritan-Bennett instrument response was linear over the concentration range used.

Blood Sampling and Handling

Aortic blood (1.5–2 mL) was drawn into heparinized syringes before induction of anesthesia, immediately after administration of anesthesia was terminated, and either 4 h after the end of anesthesia (group 1) or 24 h after induction of anesthesia (group 2). The last sampling time for group 2 was changed from that of group 1 to sample at a time likely to be at the probable peak of elevated ALT activity, to ensure we would not miss a more subtle rise in plasma ALT. Care was taken to avoid hemolysis, and samples were kept on ice until they were centrifuged at 1000 *g* for 15 min at 4°C to separate plasma. Plasma from the first eight pigs was frozen, thawed once, and analyzed for fluoride ion content (4), frozen again, then thawed and analyzed for ALT activity. Samples from the second group of pigs were thawed once before determination of ALT activity.

Alanine Aminotransferase Determination

Alanine aminotransferase activity was assayed spectrophotometrically (Baush & Lomb Spectronic 2000) at 340 nm at 30°C using Sigma Diagnostic Kit 59-10 with Sigma enzyme controls 2N and 2E and is expressed in international units per liter of plasma (U/L) (Table 1). To test whether freezing and thawing plasma altered ALT activity, before the analyses we measured the activity of ALT in pig plasma subjected to two to four freeze-thaw cycles. No change in ALT

Table 1. Alanine Aminotransferase Activity

	Group 1		Group 2		Combined groups 1 and 2	
	Desflurane	Isoflurane	Desflurane	Isoflurane	Desflurane	Isoflurane
Unanesthetized	27.0 ± 9.1 (8)	27.9 ± 8.2 (7)	29.9 ± 4.3 (5)	31.6 ± 14.4 (4)	28.1 ± 7.5 (13)	29.3 ± 10.3 (11)
Immediately after TOA	24.1 ± 5.2 (8)	27.3 ± 8.8 (7)	26.2 ± 4.3 (5)	26.6 ± 13.7 (4)	24.9 ± 4.8 (13)	27.0 ± 10.1 (11)
4 h after TOA	14.4 ± 6.1 (8)[a]	11.0 ± 8.8 (7)[a]	—	—	14.4 ± 6.1 (8)[a]	11.0 ± 8.8 (7)[a]
24 h TOA	—	—	24.2 ± 3.3 (3)	23.0 ± 6.7 (3)	24.2 ± 3.3 (3)	23.0 ± 6.7 (3)
3–8 days after induction of anesthesia	32.5 ± 2.2 (4)	25.8 ± 16.0 (3)	34.1 ± 12.8 (2)	31.0 ± 1.4 (2)	33.0 ± 6.0 (6)	27.9 ± 11.7 (5)

Values given are U/L plasma, mean ± SD. Number of pigs is given in parentheses.
TOA, termination of anesthesia.
[a] Value significantly different from other sample times within the same anesthetic group.

Table 2. Alanine Aminotransferase Activity in Pig Plasma With Elevated Alanine Aminotransferase Activity, Subjected to Repetitive Freezing and Thawing

Freeze-thaw cycle No.	Sample No.			
	1	2	3	4
1	182	200	157	177
2	177	200	158	176
3	174	200	—	—
4	170	—	—	

ALT, alanine aminotransferase.
Elevated ALT activity was obtained by adding purified ALT to normal pig plasma.

activity was observed for samples with normal or elevated (150–200 U/L) ALT activity (Table 2).

Statistical Analysis

Log transformations of the ALT data were analyzed by one-way analysis of variance and two-way analysis of variance with repeated measures. Differences between groups were tested using the Newman–Keuls method of multiple comparisons. Statistical significance was accepted at $P < 0.05$.

Results

Plasma ALT activity in samples drawn before anesthesia, at the end of anesthesia, 24 h after anesthesia (Table 1), and 3–8 days after the first exposure was not significantly different for either anesthetic group. Alanine aminotransferase activity in samples drawn 4 h after termination of anesthesia and concurrent epinephrine infusion at doses up to 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was significantly lower than at any other sample time for desflurane and isoflurane. The reduction in ALT levels was not statistically different between anesthetic groups. No significant elevation in plasma ALT activity over the baseline value was found for the pooled results of both studies (Table 1).

Discussion

The design of the present study provided a reasonable test of the potential hepatotoxicity of desflurane and isoflurane. Swine appear to be appropriate animals for studies of hepatic injury. As in humans, plasma ALT activity in pigs increases after hepatic injury (11). The anesthetic exposure (MAC-hours) of our animals exceeded by severalfold that commonly used in practice. Anesthesia was repeated, and followed an initial exposure to a halogenated anesthetic (halothane, isoflurane, or desflurane) for surgery. Our study was not designed to test for hepatic "sensitization" to anesthetics because of the low frequency of this immunologic occurrence. Epinephrine infused in group 1 animals may have decreased splanchnic blood flow and hepatic oxygenation, further adding to the potential for hepatic injury. As a further severe test, other drugs commonly used in practice were given concurrently with desflurane and isoflurane (group 2). Some of these drugs (e.g., thiopental, N_2O) produce significant cardiovascular depression under these circumstances (12). Their administration, therefore, might have decreased splanchnic blood flow and impaired hepatic oxygenation, perhaps lowering the threshold for any potential injury induced by desflurane or isoflurane. Thus, the failure to find an elevation of plasma ALT is reassuring. The substantial stability in vitro and in vivo and low solubility of desflurane and, to a lesser extent isoflurane, compared with other halogenated anesthetics may reduce or eliminate the risk of liver injury from these anesthetics.

Plasma levels of ALT associated with hepatocellular necrosis may begin to rise 1–2 h after exposure to hepatotoxins and reach a peak within 24–36 h. To ensure that we did not miss a small rise in ALT in group 1, blood was sampled 4 and 24 h after anesthesia was completed in group 2.

Aspartate aminotransferase (AST) has often been the enzyme chosen as a marker of liver damage for previous studies of anesthetic hepatotoxicity. However, we chose to measure ALT levels because increased plasma ALT is a more specific indicator of hepatic injury than is AST (13). Aspartate aminotransferase is also elevated after myocardial infarction and skeletal muscle damage. Because epinephrine infusion increases plasma AST activity (14,15), AST activity could not be used as a definitive indicator of hepatotoxicity in group 1. Acute release of ALT from necrosing tissue or during sublethal cell injury is also detectable for a longer period than is AST. Half-lives in pig plasma are 51 h for ALT and 17.4 h for AST (16).

The reduction in ALT activity in the samples drawn 4 h after administration of anesthetic was terminated (group 1) may have resulted from the infusion of large doses of epinephrine. Plasma ALT activity has been reported to decrease transiently after epinephrine administration (17).

Elevations in transaminases occur soon after toxic or circulatory hepatic disturbances (13), and usually last for only a few days. The lack of increase in ALT levels in samples drawn 3–8 days (mean, 6.1) after the first study also suggests that desflurane as well as isoflurane did not produce a delayed liver injury. Pigs in our study were followed up for an average (±SD) of 12.6 ± 3.10 days after their first exposure to a halogenated anesthetic on the day of surgery; group 1 pigs received their first exposure to desflurane an average (±SD) of 11.4 ± 2.88 days before the last samples were drawn.

Alanine aminotransferase levels in plasma from group 2 pigs that received various adjuvant drugs were not elevated over baseline values (Table 1) or different from the results for group 1. Thus, although some of these adjuvant drugs may themselves injure the liver, no hepatotoxic effect resulted from their combined use with either anesthetic. The doses of adjuvant drugs we used are thought to be clinically relevant. However, because the number of animals studied was small and the equivalence of doses (and responses) in humans and pigs may not be identical, our findings for this second group of swine are not conclusive evidence that desflurane and isoflurane combined with these adjuvants do not cause hepatic damage.

Since its introduction in 1980 isoflurane has been used extensively and it has not been shown to be an hepatotoxin (18–19). Our data did not reveal any difference between desflurane and isoflurane in their hepatic effects, despite stresses more severe than those usually clinically encountered. Neither caused hepatic injury. Based on these data, on previous toxicity studies in rats, and on the greater physical stability, lower solubility, and lesser biodegradation of desflurane relative to isoflurane, one might predict that, in humans, desflurane will be as free or possibly freer of adverse effects on the liver than isoflurane.

We thank Dr. Donald D. Koblin for his review of the manuscript. Desflurane and isoflurane were donated by Anaquest.

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Are Doppler-Detected Venous Emboli During Cesarean Section Air Emboli?

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FONG J, GADALLA F, PIERRI MK, DRUZIN M. Are Dcppler-detected venous emboli during cesarean section air emboli? Anesth Analg 1990;71:254–7.

The incidence of venous emboli during cesarean section was studied using simultaneous precordial ultrasonic Doppler monitoring and two-dimensional echocardiography. Forty-nine patients receiving either general or continuous epidural anesthesia in the horizontal position were monitored with both Doppler monitoring and echocardiography. There was excellent correlation between the embolic events detected by Doppler monitoring and by echocardiography (kappa value = 1). The incidence of venous emboli was 29% (14/49). The venous emboli detected by Doppler monitoring were indeed air emboli, not amniotic fluid or thromboemboli, as illustrated by their echocardiographic appearance.

Key Words: ANESTHESIA, OBSTETRIC. EMBOLUS, AIR—venous.

Venous emboli have been detected during cesarean section with regional and general anesthesia using precordial ultrasonic Doppler monitoring (1–3). It has been assumed that these Doppler-detected venous emboli are air emboli. During any surgical procedure, air embolism can occur if the operative field is above the level of the heart (4). However, amniotic fluid emboli also occur. Amniotic fluid can appear in the pulmonary artery blood of patients without symptoms of embolism (5). Doppler monitoring is a sensitive but nonspecific method of detecting venous emboli based on the frequency shift that occurs when sound is backscattered in relation to the velocity of particles and to the acoustical interface of these moving particles (6,7). Although air is an excellent reflector of ultrasound that changes the Doppler signal produced by blood alone, changes in blood velocity that can occur with amniotic fluid or thromboemboli can lead to a change in the audible Doppler signal. Using echocardiography, air emboli can be differentiated from amniotic fluid or from thromboemboli because of the differences in their echocardiographic appearance (8–14).

This study aimed to determine if venous emboli detected during cesarean section were air emboli and not amniotic fluid or thromboemboli.

Methods

With approval from the human rights committee of New York Hospital: Cornell and with patients' informed consent, 50 ASA physical status I or II parturients undergoing elective or emergency cesarean section with continuous lumbar epidural or general anesthesia were prospectively studied with both intraoperative Doppler monitoring and precordial two-dimensional echocardiography. All patients were in the supine horizontal position. One patient was not included in the study because signs of pregnancy-induced hypertension developed in her. We report on the remaining 49 parturients, with 42 and 7 parturients receiving continuous lumbar epidural or general anesthesia, respectively.

With the patient breathing room air, continuous lumbar epidural anesthesia was induced using either bupivacaine, lidocaine, or 2-chloroprocaine. Sensory blockade to pinprick was maintained at the level of the fourth thoracic dermatome throughout the cesarean section. General anesthesia consisted of a rapid sequence induction with preoxygenation, precura-

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rization, cricoid pressure, thiopental, and succinylcholine followed by maintenance with 50% oxygen/50% nitrous oxide mixture and 0.75% enflurane. After delivery of the baby, the patient inhaled a 30% oxygen/70% nitrous oxide mixture and received intravenous fentanyl, droperidol, and a succinylcholine infusion. Patients were mechanically ventilated with positive pressure and zero end-expiratory pressure (Ohio Anesthesia Ventilator).

All parturients were in a supine position with left uterine displacement. Using intravenous Ringer's lactate solution and ephedrine sulfate, maternal blood pressure was maintained within 20% of its preanesthetic level. Supplemental oxygen was given if the parturient's oxygen saturation decreased to 93% or below. None of the patients received transfusion of blood products. All patients received an intravenous oxytocin infusion (20 U/L of Ringer's lactate solution) immediately after the delivery of the placenta. To prevent accidental infusion of air, intravenous fluids and drugs were administered through Abbott Hemosets (model 8948).

Each patient was monitored with a precordial ultrasonic Doppler monitor (Medasonics Versatone D8), precordial two-dimensional echocardiogram (IREX 118 of Johnson & Johnson), oscillometric blood pressure cuff (Physio-Control VMS-2), electrocardiogram, skin liquid crystal temperature sticker (Clinitemp, Inc.), a Foley bladder catheter, neuromuscular stimulator (general anesthesia patients only), and finger pulse oximetry (Nellcor). Pulse oximetric hemoglobin oxygen desaturation was defined as a decrease from >97% to <95% (3).

The precordial ultrasonic Doppler transducer was placed parasternally over the fourth right intercostal space with correct transducer placement confirmed by rapidly injecting a 5-mL bolus of crystalloid solution through the patient's peripheral intravenous line (15). During the cesarean section, a Doppler monitoring change consistent with venous embolism was defined as a broken-up chirping to roaring change in the rhythmic swishing sound of the normal Doppler signal lasting at least 5 s (16). Using precordial two-dimensional echocardiography, a four-chamber view of the heart was obtained by placing the echocardiography probe at the cardiac apex. Venous emboli were diagnosed by the appearance of echogenic densities in an echolucent background of the blood-filled cardiac chamber (emboli appeared as bright white spots in the dark gray-black background) (8,9). Doppler and echocardiographic monitoring began immediately before the beginning of the cesarean section and finished immediately after skin closure at the end of the operation.

The incidence of venous embolism detection by Doppler and echocardiographic monitoring was simultaneously but independently assessed by different investigators. Using headphones, one investigator monitored the precordial ultrasonic Doppler signal and recorded all changes in hemoglobin oxygen saturation measured by finger pulse oximetry. Another investigator simultaneously recorded a precordial two-dimensional echocardiogram. The echocardiograms were taped and reviewed later by a cardiologist. All unsolicited complaints of chest pain and/or dyspnea were recorded.

Data were analyzed using the χ^2 analysis with Yates' correction or two-tailed Fisher exact test to determine the relationship between categorical variables. Comparisons of measured variables were made using the Mann–Whitney nonparametric test. $P < 0.05$ was considered statistically significant. The degree of agreement between Doppler and echocardiographic observations with respect to emboli was evaluated by using the kappa statistic (16).

Results

The demographic data in parturients with and without emboli and with general and epidural anesthesia were comparable with respect to the variables outlined in the Appendix except for the amount of preoperative fluid given. Preoperatively, patients having epidural anesthesia received an average of 2000 ± 0 mL (mean ± SD), whereas those given general anesthesia received 1714 ± 488 mL of intravenous Ringer's lactate solution ($P < 0.01$). All epidural anesthesia was continuous; however, there was no association between the embolic events and reinjection of local anesthetic into the epidural catheter.

There was perfect agreement between the incidence of venous emboli with Doppler and echocardiographic monitoring, leading to a kappa value = 1 in the 49 patients evaluated. The incidence of venous emboli was 26% (11/42) during epidural anesthesia and 42% (3/7) during general anesthesia. No statistical difference existed in the incidence of venous emboli detected related to the type of anesthesia. Embolism sometimes occurred more than once during operation and at any time. Regardless of the anesthetic technique, the incidence of embolic events in relation to surgical events was 14% before uterine incision, 7% with uterine incision, 7% with delivery of the baby, 21% with placenta removal, 71% with uterine repair, and 7% after closure of the uterine incision.

Chest pain and/or dyspnea were not significantly associated with venous emboli nor was hemoglobin oxygen desaturation. Premature ventricular contractions (in 1 of 49 patients) were not associated with emboli. In patients who had their placenta manually extracted, the incidence of emboli was not statistically different from that seen in patients in whom there was passive separation of the placenta. Similarly, the patients who had the uterus exteriorized for hysterotomy repair had an incidence of embolism comparable to those who did not. Patients with placenta previa had no increased incidence of embolism, and only one of the four patients with placenta previa had emboli.

Discussion

Our study found a 26% overall incidence of venous embolism. The embolic events occurred at any time during the cesarean section and were not associated with maternal symptoms or with hemoglobin oxygen desaturations. Doppler-detected venous emboli have been reported previously with varying incidences during cesarean section. Differences between the findings of our study and other studies may be attributable to both the differing criteria used to define a positive Doppler change and the small sample size of this study. Unlike the previous studies, our criteria for defining a positive Doppler change was a change lasting ≥5 s because Maroon et al. found that small quantities of air could lead to a readily detectable 3–5-s change in the audible Doppler signal (17). With the patient in the horizontal position, Malinow et al., Karuparthy et al., and Vartikar et al. reported incidences of 52%, 11%, and 65%, respectively (1–3). These emboli occurred during hysterotomy, delivery of the baby, placenta delivery, and hysterotomy repair. Malinow et al. and Karuparthy et al. defined a Doppler change consistent with air as a "broken up roaring" instead of the normal "swishing" sound of the precordial Doppler monitoring lasting at least 15 s. Both Malinow et al. and Vartikar et al. found that chest pain and/or dyspnea were significantly associated with venous emboli. Vartikar et al. reported that decreases in pulse oximetric hemoglobin oxygen saturations were associated with emboli.

Both echocardiography and Doppler monitoring have been shown to be sensitive indicators of venous air embolism (8,17). However, Doppler monitoring is unable to differentiate between different types of embolic material. The most likely emboli to occur during a cesarean section are air and amniotic fluid emboli, although thromboemboli are possible. Echocardiography is able to differentiate between differing types of embolic materials based on their appearance on the echocardiographic screen. When using echocardiography, amniotic fluid is not echogenic; it is echolucent (dark gray-black) as with ultrasonography (11,12). The echocardiographic acoustics of cardiac thrombi depend on their histologic composition and are seen with a heterogenicity of echocardiographic acoustics (13,14). Air is consistently highly echogenic and is seen echocardiographically as bright white spots in a dark gray-black, i.e. blood, background. In this study, there was excellent correlation between Doppler and echocardiographic detection of venous emboli. These emboli were invariably air emboli, not amniotic fluid or thromboemboli, because they were highly echogenic (8–14).

In this study, the epidural and general anesthesia groups received different amounts of preoperative fluids but had similar incidences of emboli. One possible explanation is that the sympathetic nerve blockade caused by epidural anesthesia was offset by the increased amount of preoperative intravenous fluid received, as the general and epidural anesthesia groups' hemodynamic data and incidence of intraoperative hypotension were similar.

Despite the high incidence of venous emboli during cesarean section in patients in the horizontal position, few of the emboli are hemodynamically detrimental. Therefore, viewpoints vary regarding which patients undergoing cesarean section should be monitored with a precordial ultrasonic Doppler monitor. It has been suggested that the use of this monitor might reasonably be restricted to parturients at high risk for having venous air emboli, i.e., those with severe hypovolemia, abruptio placenta, or placenta previa (4). However, others believe that this monitor should be used more frequently on patients undergoing cesarean section with regional anesthesia, as early detection is the key to successful treatment (18–20). Whether or not one chooses to monitor parturients undergoing cesarean section with a precordial Doppler monitor, we believe that the possibility of venous air embolism should be high in the differential diagnosis of sudden cardiopulmonary instability during cesarean section.

In conclusion, the incidence of venous emboli detected by simultaneous precordial Doppler monitoring and precordial two-dimensional echocardiography during cesarean section was 26%. There was perfect correlation between embolic events detected by Doppler monitoring and echocardiography. Therefore, the Doppler-detected venous emboli were air emboli, not amniotic fluid or thromboemboli, based on their echocardiographic appearance.

Appendix: Demographic Variables

1. Age
2. Height
3. Weight
4. Gravity
5. Parity
6. Reason for cesarean section
7. Incidence of active labor
8. Volume of preoperative intravenous fluids
9. Type of local anesthetic
10. Baseline systolic and diastolic blood pressure
11. Baseline pulse rate
12. Volume of intraoperative intravenous fluids
13. Method of placenta removal
14. Use of intravenous ephedrine
15. Incidence of intraoperative hypotension
16. Operative time
17. Estimated blood loss
18. Apgar scores

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Differences in Effects of Isoflurane and Enflurane on Splanchnic Oxygenation and Hepatic Metabolism in the Pig

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The effects of end-tidal concentrations of 1.45% isoflurane and 2.12% enflurane on splanchnic blood flow (electromagnetic flow probes), oxygen (O_2) extraction and surface Po_2 (Clark-type electrode), and hepatic metabolism (organic acids) were compared in an animal model relevant to humans. Eighteen laparotomized, ventilated pigs, anesthetized and paralyzed with ketamine/flunitrazepam and pancuronium, were studied. Enflurane caused significantly ($P < 0.05$) greater decreases in mean arterial pressure, cardiac output, and superior mesenteric arterial, portal, and total hepatic blood flows. In addition, hepatic arterial blood flow decreased during enflurane administration but increased markedly (40%) during isoflurane administration. However, mean surface Po_2 of liver and small intestine decreased to similar degrees (20%) during isoflurane and enflurane. Summary histograms of surface Po_2 values were leftward shifted but did not show O_2 values in the hypoxic range (0–5 mm Hg). Except for a decrease in hepatic lactate uptake during enflurane, there were no changes in either hepatic uptake or release of organic acids during anesthesia with either agent. These data show that splanchnic O_2 supply is better maintained during isoflurane than during enflurane. Although this was not reflected in differences in tissue oxygenation and metabolism, decreased portal and hepatic venous O_2 contents during enflurane indicate that an increase in preportal and hepatic oxygen extraction was necessary to preserve tissue oxygenation.

Key Words: ANESTHETICS, VOLATILE—isoflurane, enflurane. LIVER, OXYGENATION.

Intraoperative liver hypoxia is likely to contribute to postoperative hepatic dysfunction (1). Thus, choice of an anesthetic agent that interferes minimally with hepatic oxygen (O_2) supply is especially important during abdominal surgery because both laparotomy and mechanical ventilation are known to adversely affect hepatic circulation (1,2).

Previous studies have shown that halothane and enflurane decrease total hepatic blood flow and hepatic O_2 supply to various degrees (1,3–7). Compared with halothane, isoflurane appears to have less of an adverse effect on the hepatic circulation (5,6,8). The present study directly compares the effects of enflurane and isoflurane on hepatic oxygenation. Oxygen extraction of the small intestine, by affecting portal venous O_2 content, modifies hepatic O_2 supply. Knowledge of preportal O_2 extraction is therefore required to interpret adequately changes in hepatic oxygenation. Such knowledge is available for enflurane and halothane only in combination with N_2O (3,7). Nitrous oxide itself, however, leads to a decrease in hepatic blood flow and may thus obscure the effects of additional inhalation anesthetics (9).

Because changes in calculated O_2 delivery and surface Po_2 may not necessarily reflect respective changes in whole organ oxygenation (10) and function, metabolic parameters indicative of global hepatic function were determined simultaneously. This has not been done previously. The pig was chosen because of its remarkable anatomic and physiologic similarities to humans with respect to the cardiovascular and digestive systems (11–13).

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Methods

Instrumentation

The study was approved by the local committee on animal research. Twenty-five domestic pigs of either sex, weighing between 30 and 38 kg, were premedicated with intramuscular azoperon (5 mg/kg) and atropine (0.015 mg/kg). Anesthesia was induced with intravenous methomidate (6 mg/kg) administered via ear vein, and maintained by continuous intravenous infusions of ketamine (4 $mg \cdot kg^{-1} \cdot h^{-1}$) and flunitrazepam (0.0125 $mg \cdot kg^{-1} \cdot h^{-1}$). After tracheotomy, mechanical ventilation was provided by a constant-volume ventilator (Siemens, SV 900 B, Erlangen, F.R.G.) and facilitated by a continuous intravenous infusion of pancuronium (0.12 $mg \cdot kg^{-1} \cdot h^{-1}$). Respiratory rates and inspired O_2 concentration were adjusted to maintain arterial carbon dioxide tension between 38 and 42 mm Hg and arterial O_2 tension between 95 and 110 mm Hg. End-tidal concentrations of the inhalation anesthetics were measured by multigas analyzer (Datex, Normac, model AA-102-23-00, Finland). After a 30-min warm-up period the Normac was zeroed against room air and calibrated using a standard calibration gas according to manufacturer's specification. All animals were in the supine horizontal position. Body temperature was continuously monitored by a thermistor of a flow-directed thermodilution catheter (Edwards Laboratory, model 93A-131-7F) and was kept constant by placing the animals on a heating pad and by warming the inspired gases. Catheters were inserted into the abdominal aorta via the left femoral artery (Braun, 16 gauge Cavafix-Certo, Melsungen, F.R.G.), into the pulmonary artery (Edwards Laboratory, model 93A-131-7F), and the superior vena cava (Braun, 16 gauge Cavafix-Certo) via right and left jugular internal veins (Braun, Cavafix-Certo). All animals received 10–15 $mL \cdot kg^{-1} \cdot h^{-1}$ of Ringer's solution to maintain central venous pressure constant.

After median laparotomy, the left hepatic vein was cannulated via transhepatic puncture (14) (Braun, 18 gauge Vasofix Braunüle). Correct position of the cannula tip in the main stem of the two hepatic veins was verified at autopsy. The portal vein was cannulated (Vygon, 20 gauge Leader Cath 115, Ecouen, France) using Seldinger's technique.

Precalibrated electromagnetic flow probes (Stölzer Messtechnik, Waldkirch, F.R.G.) of appropriate sizes to ensure a snug fit were placed around the hepatic artery, the portal vein, and the superior mesenteric artery. Care was taken to preserve the periarterial nerve plexus. The flow probes were connected to flow meters with incorporated nonocclusive zero (Hellige, Freiburg, F.R.G.), which was rechecked repeatedly during the experiment. The superior gastroduodenal artery was ligated to ensure that true hepatic blood flow was measured.

Hemodynamic Measurements

Intravascular catheters were connected to pressure transducers (Senso Nor, type 840, Horten, Norway). A multichannel recorder (Hellige) was used for the recording of signals. Cardiac output was determined by thermodilution technique (Siemens, CO Computer model 404-1, Erlangen, F.R.G.). The mean value of triplicate injections of 5 mL of ice-cold, temperature-monitored saline was considered to reflect actual cardiac output if the measurements were within a range of ±5% from the calculated mean.

Total hepatic blood flow was calculated as the sum of hepatic arterial and portal venous blood flow. Vascular resistances (systemic, hepatic arterial, portal venous, and superior mesenteric arterial) were calculated using the formulas listed in the Appendix. Heart rate was derived from the R-R intervals of an extremity electrocardiogram.

Determination of Oxygen Supply/Uptake

Blood gas tensions, pH, and calculated O_2 saturation were determined using an ABL 3 autoanalyzer (Radiometer, Copenhagen, Denmark). Hemoglobin was measured by the cyan methemoglobin method. Oxygen contents, O_2 deliveries, O_2 uptakes, and O_2 extraction ratios were derived from the formulas listed in the Appendix.

Preliminary studies had shown that there were no differences between portal and mesenteric venous O_2 content. Thus, portal venous O_2 content was used for the calculation of the small intestine O_2 uptake (see Appendix).

Determination of Surface Po_2 of Liver and Small Intestine

Surface Po_2 of liver and small intestine were measured simultaneously using a multiwire platinum electrode, as described previously (15,16). Preliminary studies had shown that placement of the electrodes at different areas of the liver and small intestine surfaces produced comparable results. At each stage a total of about 100 individual Po_2 measurements were obtained at 10–15 different electrode

Table 1. Baseline Values Before Administration of Volatile Anesthetics

Variables	Pre-Isoflurane	Pre-Enflurane
Intravascular pressure		
Mean arterial (mm Hg)	97 ± 16	89 ± 9
Central venous (mm Hg)	2.6 ± 0.7	3.5 ± 1.5
Portal venous (mm Hg)	5.1 ± 1.1	6.2 ± 1.9
Hepatic venous (mm Hg)	2.4 ± 0.5	3.8 ± 1.5
Blood flow		
Cardiac output (L/min)	4.6 ± 1.6	5.2 ± 0.6
Total hepatic (mL/min)	800.1 ± 165.5	919.1 ± 141.8
Hepatic arterial (mL/min)	96.1 ± 32.3	144.6 ± 52.4
Portal venous (mL/min)	704.4 ± 148.7	774.4 ± 132.6
Superior mesenteric arterial (mL/min)	556.7 ± 112.8	591.1 ± 154.1
Vascular resistance		
Systemic arterial (U)	23 ± 8	17 ± 2
Hepatic arterial (U)	1123 ± 552	651 ± 219^{a}
Portal venous (U)	4 ± 2	3 ± 2
Superior mesenteric arterial (U)	171 ± 47	150 ± 48
Oxygen content		
Systemic arterial (mL/100 mL)	13.3 ± 1.3	13.0 ± 0.8
Portal venous (mL/100 mL)	10.9 ± 1.4	10.5 ± 1.1
Hepatic venous (mL/100 mL)	9.2 ± 1.5	7.3 ± 2.5
Oxygen delivery		
Total hepatic (mL/min)	89.5 ± 19.6	100.3 ± 15.9
Hepatic arterial (mL/min)	12.6 ± 4.2	19.0 ± 7.0
Portal venous (mL/min)	76.8 ± 16.9	81.3 ± 14.3
Superior mesenteric arterial (mL/min)	74.2 ± 16.0	76.8 ± 18.7
Oxygen uptake		
Total hepatic (mL/min)	16.0 ± 7.5	32.0 ± 13.2^{a}
Small intestine (mL/min)	13.4 ± 4.7	14.2 ± 3.0
Oxygen extraction ratio		
Total hepatic	0.18 ± 0.06	0.34 ± 0.20
Small intestine	0.19 ± 0.04	0.19 ± 0.06
Tissue surface PO_2		
Liver (mm Hg)	71.0 ± 5.0	65.5 ± 8.4
Small intestine (mm Hg)	66.4 ± 4.9	64.4 ± 6.0
Hepatic uptake		
Pyruvate (μmol/min)	15 ± 38	24 ± 12
Lactate (μmol/min)	485 ± 437	697 ± 438
Hepatic release		
β-OH-butyrate (μmol/min)	9 ± 15	12 ± 15
Acetoacetate (μmol/min)	9 ± 6	14 ± 10
Miscellaneous		
Heart rate (beats/min)	92 ± 13	103 ± 11
Hematocrit (%)	30.5 ± 3.5	29.1 ± 2.5

Values are mean ± SD. Note that baseline values were obtained during laparotomy and ketamine/flunitrazepam anesthesia.

$^{a}P < 0.05$ compared with pre-isoflurane.

Table 2. Percent Changes From Baseline Values

Variables	Isoflurane	Enflurane
Heart rate	+8.7 ± 4.7	−27.9 ± 4.7^{a,b}
Intravascular pressure		
Central venous	−5.6 ± 7.8	+74.8 ± 18.9^{a,b}
Portal venous	−5.8 ± 5.6	+29.9 ± 9.3^{a,b}
Hepatic venous	−3.7 ± 3.7	+71.7 ± 19.1^{a,b}
Vascular resistance		
Systemic arterial	−15.8 ± 6.0^{b}	−1.5 ± 7.9
Hepatic arterial	−50.1 ± 3.9^{b}	−25.4 ± 3.5^{a,b}
Portal venous	+22.6 ± 15.7	+19.3 ± 29.2
Superior mesenteric arterial	−13.7 ± 6.8	−17.0 ± 8.0
Oxygen content		
Hepatic venous	−0.9 ± 5.4	−45.6 ± 8.1^{a,b}
Oxygen delivery		
Hepatic arterial	+43.9 ± 8.5^{b}	−40.8 ± 5.9^{a,b}
Portal venous	−23.6 ± 3.5	−54.4 ± 3.4^{a,b}
Oxygen extraction ratio		
Total hepatic	+7.7 ± 13.1	+92.7 ± 27.8^{a,b}
Small intestine	+26.9 ± 12.7	+68.8 ± 11.9^{a,b}
Tissue surface Po_2		
Liver	−24.7 ± 15.2^{b}	−20.4 ± 14.0^{b}
Small intestine	−19.8 ± 14.9^{b}	−17.8 ± 13.0^{b}

Values are mean ± SD.

$^{a}P < 0.05$ compared with isoflurane.

$^{b}P < 0.05$ compared with no change.

locations. The distribution of these values, illustrated as summary surface Po_2 histograms, reflects tissue oxygenation, which is the net result of nutritive blood flow and tissue O_2 consumption (17).

Determination of Hepatic Metabolic Function

Arterial, portal venous, and hepatic venous blood samples were collected for determination of lactate, pyruvate, β-OH-butyrate, and acetoacetate concentrations. These substances were determined enzymatically as previously described (18). Hepatic uptake of lactate and pyruvate and hepatic release of β-OH-butyrate and acetoacetate were calculated using formulas listed in the Appendix.

Experimental Protocol

At the end of the surgical preparation, at least 30 min were allowed before baseline readings during ketamine/flunitrazepam anesthesia were obtained. Subsequently, in nine animals each end-tidal concentrations of either 1.45% isoflurane or 2.12% enflurane were kept constant over a period of 50–60 min. Measurements were repeated after hemodynamic stabilization.

In seven additional animals, the effects of time on the stability of the surgical preparation were evaluated during baseline anesthesia (ketamine/flunitrazepam). The surgical preparation was performed as described earlier. No interventions were undertaken after baseline readings had been obtained, and repeat measurements were made 2 h later.

Statistical Analysis

The data were statistically analyzed by Student's *t*-test (comparisons within groups) and by one-way

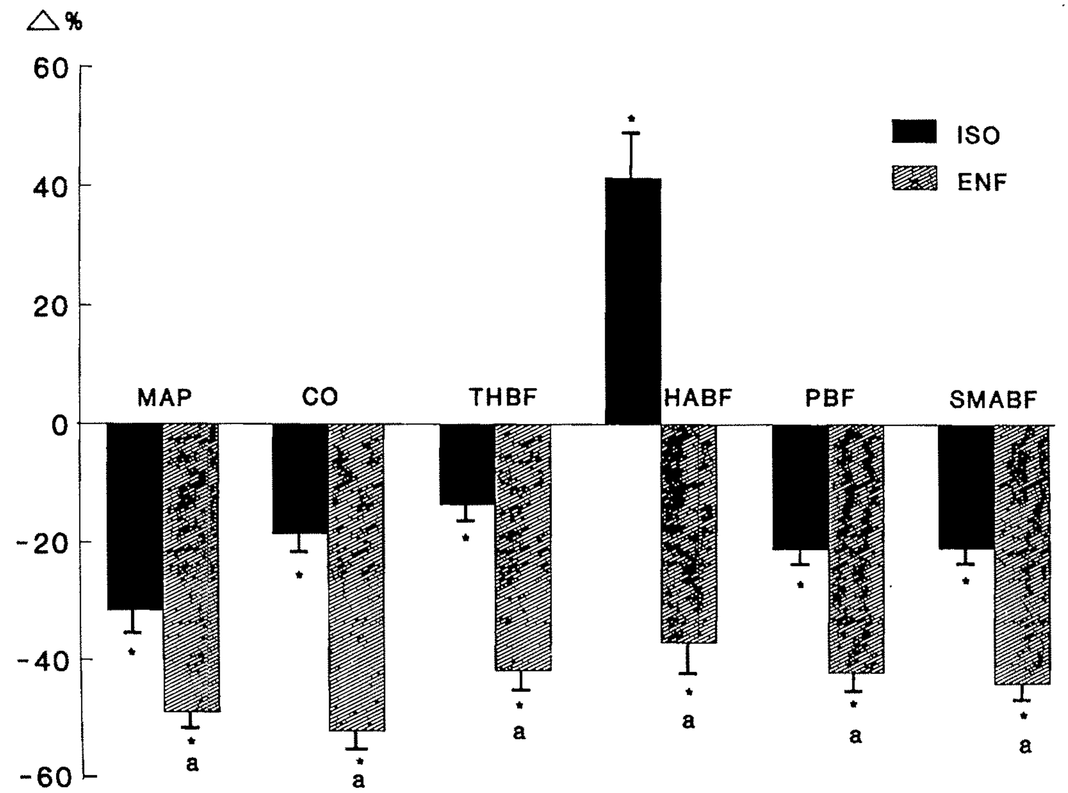

Figure 1. Percent changes from baseline values (Table 1) in systemic and splanchnic hemodynamics during isoflurane and enflurane. *$P < 0.05$ compared with no (zero) change. $^{a}P < 0.05$ compared with isoflurane. MAP, mean arterial pressure; CO, cardiac output; THBF, HABF, PBF, and SMABF, total hepatic, hepatic arterial, portal, and superior mesenteric arterial blood flow.

analysis of variance and Bonferroni's *t*-test (comparisons between groups). A *P* value of <0.05 was considered statistically significant.

Results

Baseline values for each experimental group are listed in Table 1. There were only few differences between pre-isoflurane and pre-enflurane (hepatic arterial vascular resistance, total hepatic O_2 uptake).

Percent or absolute changes from baseline values for each experimental group are shown in Table 2 and Figures 1 through 3. Both inhalation anesthetics caused significant decreases in mean arterial pressure and cardiac output that were more pronounced (50%) during enflurane (Figure 1). Heart rate remained unchanged during isoflurane, but it decreased during enflurane anesthesia (Table 2). Central venous, hepatic venous, and portal venous pressures remained unchanged during isoflurane, but they increased during enflurane (Table 2).

Whereas total hepatic, portal venous, and superior mesenteric arterial blood flow decreased during both agents (Figure 1), hepatic arterial blood flow increased markedly (42%) during isoflurane but decreased (37%) during enflurane. As a consequence, hepatic arterial blood flow expressed as a fraction of total hepatic blood flow increased (60%) during isoflurane and did not change during enflurane anesthesia. Total hepatic blood flow expressed as a fraction of cardiac output remained unchanged during anesthesia with both agents. In contrast, the fraction of cardiac output going to the superior mesenteric artery increased by 20% during enflurane and remained unchanged during isoflurane anesthesia.

There were also differences in the effects of vascular resistances, (a) between agents and (b) between regions. Whereas hepatic arterial vascular resistance decreased during both agents (isoflurane > enflurane), systemic vascular resistance decreased during anesthesia with isoflurane only (Table 2). Portal venous and superior mesenteric arterial vascular resistances remained unchanged during both agents.

With the exception of hepatic arterial O_2 delivery during isoflurane (44% increase), O_2 deliveries fell uniformly (Table 2, Figure 2). This effect was more pronounced during enflurane. In spite of differences

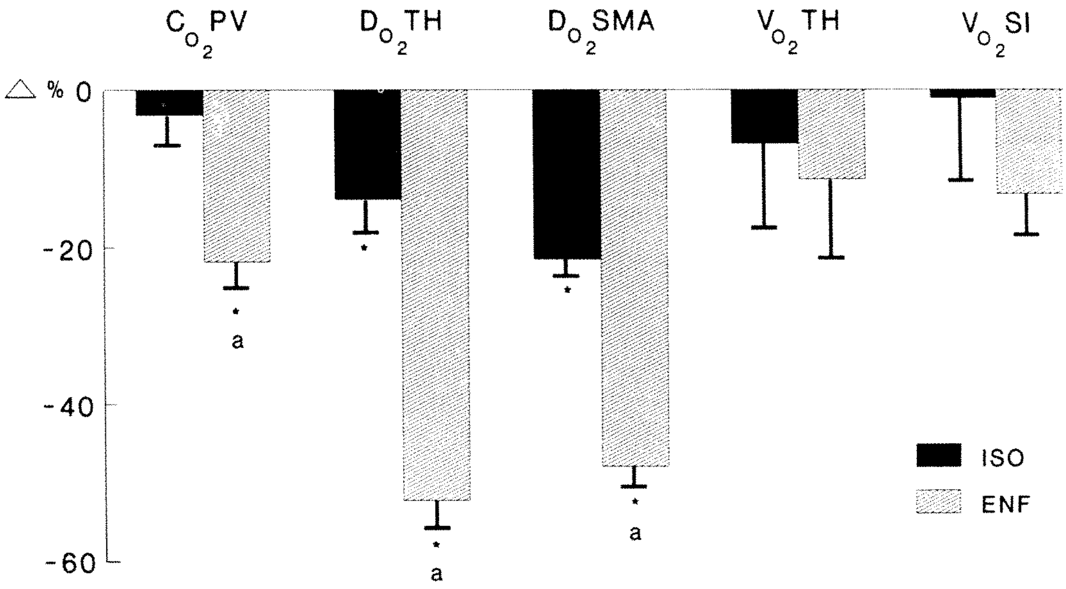

Figure 2. Percent changes from baseline values (Table 1) in hepatic and small intestine oxygen supply and uptake during isoflurane and enflurane. Co_2PV, portal venous O_2 content; Do_2TH and Do_2SMA, total hepatic and superior mesenteric arterial O_2 delivery; Vo_2TH and Vo_2SI, total hepatic and small intestine O_2 uptake.

in O_2 contents (portal and hepatic venous) and O_2 deliveries (total hepatic, portal venous, and superior mesenteric arterial) between isoflurane and enflurane, O_2 uptake of liver and small intestine remained unaffected during both agents (Figure 2). However, because of differences in O_2 deliveries, O_2 extraction ratios of liver and small intestine (Table 2) increased by 50%–90% during enflurane but remained unchanged during isoflurane.

With the exception of hepatic arterial blood flow, which showed a negative correlation ($r = -0.84$, $P = 0.003$) with cardiac output during isoflurane and a positive correlation ($r = 0.79$, $P = 0.007$) with mean arterial pressure during enflurane, there were no statistically significant relationships between changes in splanchnic blood flow and changes in cardiac output or mean arterial pressure.

During isoflurane and enflurane mean Po_2 values on the surfaces of liver and small intestine decreased by approximately 20% (Table 2). In addition, the summary Po_2 histograms showed leftward shifts (Figures 4 and 5). However, there were no Po_2 values in the hypoxic or anoxic ranges (0–5 mm Hg).

Except for a decrease in hepatic uptake of lactate during enflurane, there were no significant changes in either hepatic uptake (lactate, pyruvate) or release (β-OH-butyrate, acetoacetate) during isoflurane and enflurane (Figure 3). Hematocrit remained unchanged throughout (Table 2).

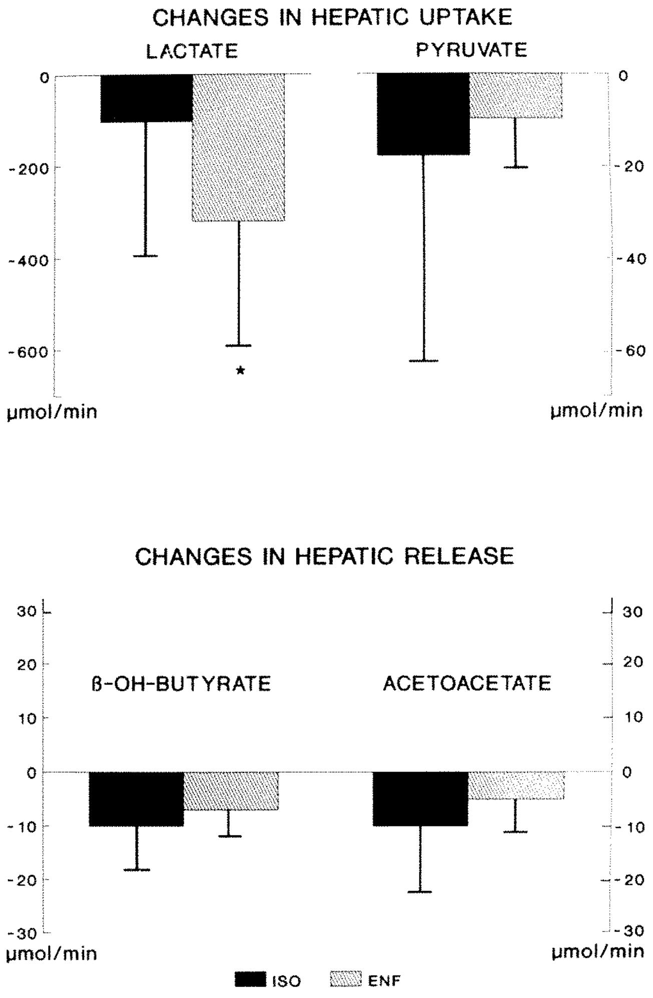

Figure 3. Changes (μmol/min) in hepatic lactate and pyruvate uptake, and in β-OH-butyrate and acetoacetate release. $^*P < 0.05$ compared with no change.

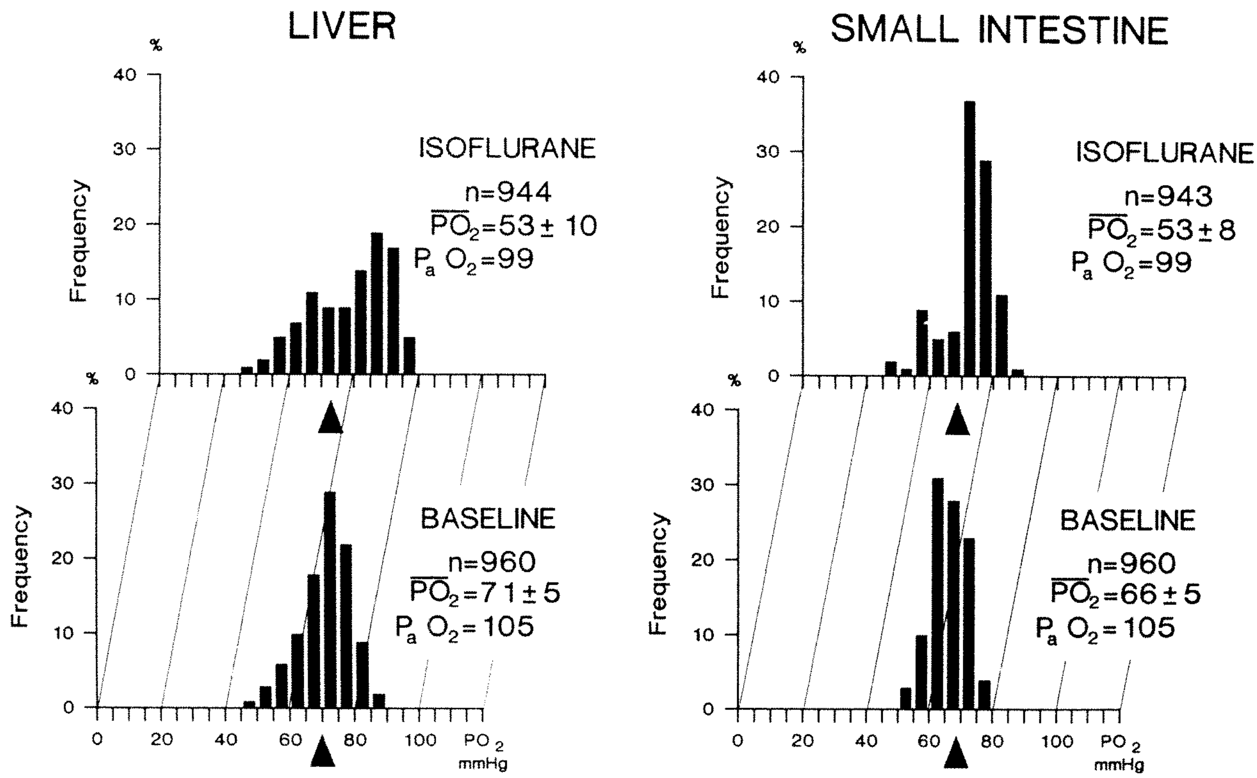

Figure 4. Summary histograms of liver and small intestine surface Po$_2$ from nine pigs during baseline and 1 MAC isoflurane anesthesia: *n* indicates the total number of measurements; $\overline{\text{Po}_2}$ the mean tissue Po$_2$; and Pao$_2$ the mean arterial Po$_2$ during recording of the histograms. Note the lack of hypoxic Po$_2$ ranges (0–5 mm Hg) despite a concomitant leftward shift and a decrease in $\overline{\text{Po}_2}$ (▲).

In the control animals, except for an increase in hepatic venous O$_2$ content (from 7.7 ± 2.1 to 9.2 ± 1.8 mL/100 mL; $P < 0.05$), there were no statistically significant differences between control values and those obtained 2 h later.

Discussion

The principal findings of this study are (a) lesser decrease in splanchnic O$_2$ delivery during isoflurane than during enflurane anesthesia; (b) increase in hepatic arterial blood flow during isoflurane only; (c) increased O$_2$ extraction ratios of liver and small intestine and decreased portal and hepatic venous O$_2$ contents during enflurane; (d) leftward shift of the summary Po$_2$ histograms but without Po$_2$ values in the hypoxic ranges during anesthesia with either agent; and (e) little change in hepatic metabolic function during enflurane.

Critique of Methods

These studies were conducted in anesthetized and ventilated pigs during laparotomy. The pig was chosen because of its anatomic and physiologic similarities to humans, particularly with respect to liver enzyme systems (11–13,19). Both laparotomy and mechanical ventilation are known to interfere with splanchnic perfusion (1,2). In contrast to barbiturates (1,20) and opiates (1,21), ketamine has no or little effect on liver and preportal circulation (22). The same is true for pancuronium (23). The effects of flunitrazepam on the splanchnic circulation are unknown. It should, therefore, be realized that the effects associated with isoflurane and enflurane occurred during a baseline anesthesia with ketamine and flunitrazepam, and during surgery. This, however, mimics the clinical situation in which patients receive a baseline anesthesia during laparotomy to which an inhalation anesthetic may subsequently be added to deepen the anesthetic state.

The protocol required extensive surgical preparation. Both baseline anesthesia and surgery might have resulted in spontaneous deterioration of the preparation over time and may thus have influenced the results. However, the data obtained in control animals indicate that significant spontaneous deterioration of the preparation can be ruled out.

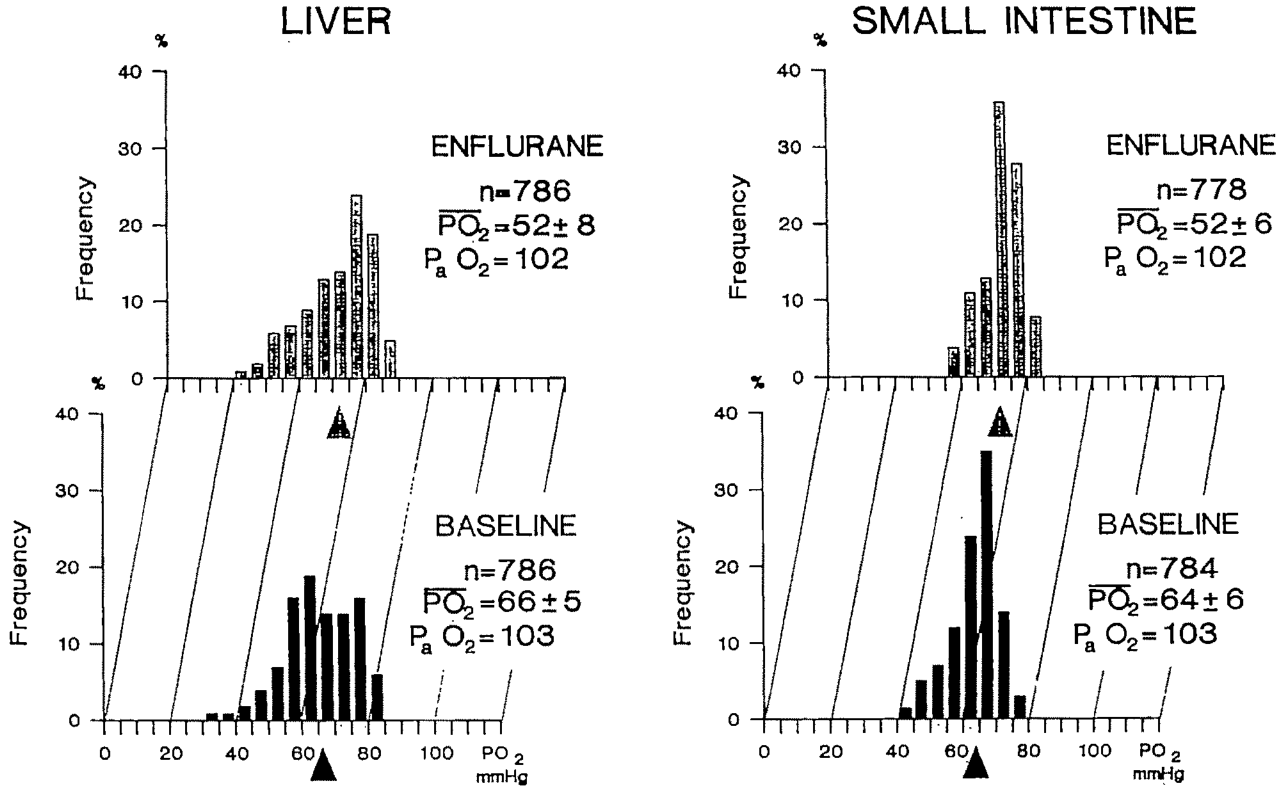

Figure 5. Summary histograms of liver and small intestine surface Po_2 from nine pigs during baseline and 1 MAC enflurane anesthesia. As in Figure 4, no hypoxic Po_2 values occurred despite leftward shifts of the surface Po_2 histograms.

The concentration of 1.45% isoflurane used corresponds to 1 MAC in pigs (11). Because MAC values for enflurane have not been established in the pig, and because the MAC value for isoflurane in pigs (11) is comparable to that in the dog (24), we used the canine MAC value for enflurane (25) in pigs. On the basis of recently revised MAC values for isoflurane in pigs (26), it is possible that the end-tidal concentrations used in this study may be somewhat lower than 1 MAC.

The transparenchymatous cannulation of the left hepatic vein was performed as previously described (14). Correct position of the catheter tip in the region where the four hepatic veins merge was verified at autopsy. This technique allows collection of mixed venous hepatic blood while avoiding ventilation-related changes in catheter position and partial occlusion of hepatic venous outflow sometimes associated with hepatic vein catheterization via internal jugular vein (14).

The portal vein was catheterized using Seldinger's technique. Preliminary studies had shown identical portal venous flows before and after portal vein catheterization, thus excluding vascular obstruction by the catheter.

The technique of measuring surface Po_2 using O_2-sensitive multiwire surface electrodes has been well established (15,16). Although surface Po_2 may not necessarily reflect whole organ Po_2, this technique allows determination of tissue Po_2 without causing tissue trauma or interference with the microcirculation (16). Whereas polarographic reduction of halothane at the Po_2 electrode yields artificially elevated Po_2 values (27), isoflurane and enflurane do not interfere with this technique (16).

Effects of Inhalation Anesthetics on Systemic Hemodynamics

Systemic arterial hypotension and decrease in cardiac output was greater during enflurane than during isoflurane. The decreases in mean arterial pressure and cardiac output during isoflurane and enflurane are quantitatively comparable to those reported by other investigators (4–7,11).

Effects of Inhalational Agents on Splanchnic Blood Supply

Total hepatic and portal blood flows decreased during both inhalation anesthetics but to a lesser degree during isoflurane. This is consistent with previous findings (1,28). The decrease in portal blood flow during isoflurane was accompanied by a 42% increase in hepatic arterial blood flow. This is in agreement with findings in nonlaparotomized animals (5,11,29), but not with findings in laparotomized miniature pigs where a decrease in hepatic arterial blood flow was observed (8).

Usually, hepatic arterial vascular resistance decreases and hepatic arterial blood flow increases in response to a decrease in portal blood flow (30). Previous studies suggest that this compensatory mechanism is preserved during isoflurane in the absence of surgical stress, but is lost when surgical stress is added (5,8,11). We cannot confirm the latter finding. With comparable reductions in mean arterial pressure and cardiac output, we found a marked decrease in hepatic arterial vascular resistance and marked increases in hepatic arterial blood flow during isoflurane even during laparotomy. It thus appears that during isoflurane anesthesia, the "hepatic buffer response" (31) is maintained even in the presence of abdominal surgical stress. Differences in results may be related to differences in species, baseline anesthesia, and method of measuring blood flow.

In contrast, during enflurane we found a decrease in hepatic arterial blood flow. This may be related in part to a greater decrease in cardiac output and mean arterial pressure during enflurane. However, a decrease in hepatic arterial vascular resistance during enflurane also might indicate that the semireciprocity of flow was even maintained during enflurane. These findings are in accordance with previous results (4,7,28).

Our observation of decreases in superior mesenteric arterial blood flow during both anesthetics is consistent with previous results (7,32). Few correlations were found between changes in systemic and regional hemodynamics. Only hepatic arterial blood flow correlated with changes in cardiac output during isoflurane and with changes in mean arterial pressure during enflurane. This would suggest that during both anesthetics splanchnic perfusion is little dependent on changes in systemic hemodynamics.

Effects of Inhalational Agents on Splanchnic Oxygen Consumption and Tissue Oxygenation

Oxygen uptake by liver and small intestine remained unchanged during both agents. This is consistent with previous findings during enflurane (7) and during isoflurane (8). In contrast, studies in an isolated small intestine loop preparation showed a decrease in small intestine O_2 uptake during isoflurane (32).

There was a uniform decrease in O_2 delivery to liver and small intestine during administration of both anesthetic agents. However, these decreases were less pronounced during isoflurane (14%–21%) than during enflurane (~50%). The quantitative differences in O_2 deliveries to liver and small intestine were due to more pronounced decreases in hepatic and superior mesenteric arterial blood flow, and, additionally, to a decrease in portal venous O_2 content during enflurane. Furthermore, there was a possibly compensatory increase in hepatic arterial blood flow and thus in hepatic arterial O_2 delivery during isoflurane only.

The significant decreases in portal and hepatic venous O_2 contents during enflurane reflect the marked increases in O_2 extraction ratios of small intestine and liver during enflurane in response to the decreases in O_2 deliveries to small intestine and liver. These results are supported by previous studies (7). We found, as have others, no change in O_2 extraction ratios of small intestine and liver and, thus, in portal and hepatic venous O_2 contents during isoflurane (8). In contrast to these findings, decreased hepatic venous Po_2 as a result of reduced O_2 supply through the portal vein during isoflurane has recently been reported (16). Differences in results may, again, be related to differences in species and baseline anesthesia. Greater O_2 extraction ratios of liver and small intestine, and lower portal and hepatic venous O_2 contents during enflurane compared with isoflurane were not reflected in differences in surface Po_2 and Po_2 histograms of liver and small intestine. During both enflurane and isoflurane, surface Po_2 of liver and small intestine decreased similarly (~20%), and there were comparable leftward shifts of the Po_2 histograms. However, hypoxic Po_2 values (0–5 mm Hg) were not observed. The absence of hypoxic Po_2 values (especially during enflurane) suggests that the increases in O_2 extractions sufficiently compensated for the decreases in O_2 deliveries. However, it cannot entirely be ruled out that liver surface Po_2 values are not entirely representative of whole organ oxygenation. Due to species-related distributions of hepatic arterial and portal blood flow, surface Po_2 values may reflect primarily hepatic arterial blood flow (33). In addition, in pigs the liver capsule contains a dense arterial network (34). Relatively high mean surface Po_2 values and a rightward localization of the Po_2 histograms during baseline conditions would support such possibilities.

In contrast to our findings, and in agreement with species-related differences in liver blood flow distribution in a dog model hypoxic (0–5 mm Hg) surface Po_2 values were observed in 8% of all Po_2 measurements during piritramid baseline anesthesia and in 20% of all measurements during 1 MAC isoflurane (16). The effects of enflurane had not been studied. Data on the effects of volatile anesthetics on surface Po_2 of the small intestine are not available for comparison.

Effects of Inhalational Agents on Hepatic Metabolic Function

Except for a decrease in hepatic lactate uptake during enflurane, there were no significant changes in either hepatic uptake of lactate and pyruvate or hepatic release of β-OH-butyrate and acetoacetate during administration of the two agents. This would suggest that the intermediary metabolism of the liver was not adversely affected. The isolated reduction in lactate uptake during enflurane may reflect the greater decrease in total hepatic blood flow resulting in decreased lactate delivery to the liver.

In conclusion we have shown that splanchnic O_2 delivery is better preserved during isoflurane than during enflurane anesthesia. This may in part be related to lesser depression of cardiac output and mean arterial pressure, and to an increase in hepatic arterial blood flow during isoflurane. The differences in O_2 transport between isoflurane and enflurane were not reflected in differences in surface Po_2 levels and global hepatic function. However, during enflurane anesthesia preportal and hepatic oxygen extraction ratios increased, indicating that compensatory mechanisms were activated to preserve tissue oxygenation. Thus, for clinical practice, in patients with critical splanchnic perfusion isoflurane might be the preferred volatile anesthetic.

Appendix

The formulas applied in the text are given below.

Vascular Resistances

$$\mathrm{SVR\ (U)} = \frac{\mathrm{MAP\ (mm\ Hg) - CVP\ (mm\ Hg)}}{\mathrm{CO\ (L/min)}},$$

$$\mathrm{HAVR\ (U)} = \frac{\mathrm{MAP\ (mm\ Hg) - HVP\ (mm\ Hg)}}{\mathrm{HABF\ (mL/min)}} \times 10^3,$$

$$\mathrm{PVVR\ (U)} = \frac{\mathrm{PVP\ (mm\ Hg) - HVP\ (mm\ Hg)}}{\mathrm{PBF\ (mL/min)}} \times 10^3,$$

$$\mathrm{SMAVR\ (U)} = \frac{\mathrm{MAP\ (mm\ Hg) - PVP\ (mm\ Hg)}}{\mathrm{SMABF\ (mL/min)}} \times 10^3,$$

where SVR, HAVR, PVVR, and SMAVR are the systemic, hepatic arterial, portal venous, and superior mesenteric arterial vascular resistances; MAP, CVP, PVP, and HVP are the mean arterial, central venous, portal venous, and hepatic venous pressures; CO is the cardiac output; HABF, PBF, and SMABF are the hepatic arterial, portal venous, and superior mesenteric arterial blood flows.

Oxygen Supply/Uptake

$$O_2\ \mathrm{content} = \mathrm{Hb} \cdot O_2\ \mathrm{saturation} \cdot 1.34 + Po_2 \cdot 0.0031,$$

$$O_2\ \mathrm{delivery} = O_2\ \mathrm{content} \cdot \mathrm{flow},$$

$$Do_2TH = Do_2HA + Do_2PV,$$

$$Do_2HA = Co_2A \cdot \mathrm{HABF} \times 10^{-2},$$

$$Do_2PV = Co_2PV \cdot \mathrm{PBF} \times 10^{-2},$$

$$Do_2SMA = Co_2A \cdot \mathrm{SMABF} \times 10^{-2},$$

$$Vo_2TH = (Co_2PV - Co_2HV) \cdot \mathrm{PBF} \times 10^{-2} + (Co_2A - Co_2HV) \cdot \mathrm{HABF} \times 10^{-2},$$

$$Vo_2SI = (Co_2A - Co_2PV) \cdot \mathrm{SMABF} \times 10^{-2},$$

$$Eo_2TH = Vo_2TH/Do_2TH,$$

$$Eo_2SI = Vo_2SI/Do_2SMA,$$

Do_2TH, Do_2HA, Do_2PV, and Do_2SMA are the total hepatic, hepatic arterial, portal venous, and superior mesenteric arterial O_2 deliveries; Co_2A, Co_2PV, and Co_2HV are the systemic arterial, portal venous, and hepatic venous O_2 contents; Vo_2TH and Vo_2SI are the total hepatic and small intestine O_2 uptake; and Eo_2TH and Eo_2SI are the total hepatic and small intestine O_2 extraction ratios.

Hepatic Metabolism

Hepatic lactate uptake

$$= (C_{LAC}PV - C_{LAC}HV) \cdot \mathrm{PBF} + (C_{LAC}HA - C_{LAC}HV) \cdot \mathrm{HABF}.$$

Hepatic pyruvate uptake

$$= (C_{PYR}PV - C_{PYR}HV) \cdot \mathrm{PBF} + (C_{PYR}HA - C_{PYR}HV) \cdot \mathrm{HABF}.$$

Hepatic β-OH-butyrate release

$$= (C_{BUT}HV - C_{BUT}PV) \cdot \mathrm{PBF} + (C_{BUT}HV - C_{BUT}HA) \cdot \mathrm{HABF}.$$

Hepatic acetoacetate release

$$= (C_{ACE}HV - C_{ACE}PV) \cdot \mathrm{PBF} + (C_{ACE}HV - C_{ACE}HA) \cdot \mathrm{HABF}.$$

C_{LAC}, C_{PYR}, C_{BUT}, and C_{ACE} are the lactate, pyruvate, β-OH-butyrate, and acetoacetate concentrations in hepatic arterial (HA), portal venous (PV), and hepatic venous (HV) blood.

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Effects of Alfentanil on Isolated Cardiac Tissues of the Rabbit

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Alfentanil causes cardiac stimulation or depression in intact animals and in clinical practice; there is no information concerning its direct effects on the heart. Therefore, we studied the effects of alfentanil on isolated cardiac tissues from young adult rabbits. The right atrium with sinoatrial node (SA node) was beating spontaneously, and the left atrium and papillary muscle were stimulated. Isometric contraction was monitored. Alfentanil, in concentrations of 0.05–0.5 mM, decreased by 6%–55% the frequency of contractions of the right atrial-SA node in a dose-related manner. In left atria and right atrial-SA node, but not in papillary muscle, alfentanil in concentrations ≥0.01 mM increased the peak developed force and its maximum rate of increase. The time-to-peak developed force was prolonged in papillary muscle but not in right atrial-SA node and left atria. The maximum rate of fall of peak developed force was increased in left atria and decreased in papillary muscle by the administration of alfentanil. The time-to-50% relaxation of peak developed force was not consistently affected by alfentanil in all three muscle preparations. The same concentrations of alfentanil (≥0.01 mM) increased resting force in papillary muscle but not in left atria or right atrial-SA node. It is concluded that alfentanil has direct positive inotropic and negative chronotropic effects on the heart and that it causes contracture of ventricular myocardium.

Key Words: ANALGESICS, ALFENTANIL. HEART, MYOCARDIAL FUNCTION—alfentanil.

The synthetic narcotic alfentanil is a tetrazole derivative of fentanyl. Its analgesic action is rapid in onset, short in duration, and more potent than morphine (for review see References 1 and 2). Fentanyl and its derivatives alfentanil and sufentanil have been used in animal studies and clinical practice for anesthetic induction and supplementation, and, because cardiovascular stability can be maintained with doses as high as 50 times the effective surgical dose, as a general anesthetic combined with nitrous oxide (3–8). However, a dose-related, transient cardiac stimulation has been observed in intact dogs (3). At high doses (5 mg/kg, intravenous bolus), increased cardiac stimulation occurs, associated with increased systemic vascular resistance and decreased heart rate and cardiac output (3). High-dosage alfentanil anesthesia has also been shown in rats to produce marked decreases in mean arterial pressure and heart rate, which is believed to be due to alfentanil-induced attenuation of sympathetic outflow (4). Clinically, fentanyl-derived analgesics cause bradycardia or sinus arrest, which has been attributed to increased vagal tone (5). In clinical studies and intact whole animal, the responses are complicated by several factors such as age, disease state, presence of other drugs, route and rate of administration, reflex mechanisms, and the preload and afterload of the heart. Thus, whether or not alfentanil has a direct effect on the heart cannot be definitely derived from the above in vivo studies. Accordingly, the purpose of this study was to define the direct effects of alfentanil on the heart. In our laboratory, we have observed that there are different responses in isolated cardiac tissues to drugs such as protamine (6). This study was intended to compare the direct effects of alfentanil on contraction of atrial and ventricular myocardium, and on sinus node rate. Therefore, we examined the chronotropic effects of alfentanil on isolated spontaneously beating right atrial-sinoatrial node preparation and inotropic effects on isolated left atria and papillary muscle from young adult rabbits.

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Methods and Materials

Isolated Cardiac Tissues

The study was approved by the institutional animal investigation committee of the University of Washington. Preparation of the isolated cardiac tissues has been previously described (6–8). Rabbits weighing 1.5–1.9 kg were killed by a captive bolt pistol followed by exsanguination. The hearts were quickly removed and put in an oxygenated Krebs' solution. The right atrium with sino-atrial node, left atrium, and right ventricular papillary muscle were rapidly isolated and placed in a Blinks' dual tissue bath (9) containing Krebs' solution oxygenated with 95% O_2/5% CO_2, having a pH adjusted to 7.4, and with temperature maintained at 30°C. The composition of the Krebs' solution (in mM) was NaCl 121, KCl 2.4, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 22, KH_2PO_4 1.2, and glucose 11.2. The lower end of each tissue was fixed to a punctate stimulating electrode and the upper end was attached to a Statham G7B force transducer with 4-0 silk thread. The right atria were beating spontaneously. Left atria and papillary muscles were stimulated electrically with a square-wave DC impulse of 4-ms duration; voltage was double the threshold value for the papillary muscles at 0.2 Hz and for the left atria at 1 Hz. Each muscle preparation was stretched to a muscle length at which peak developed force was achieved. Isometric force of contraction was recorded continuously on a Gould 2400S four-channel recorder.

Experimental Protocol

The preparation was equilibrated for 45–60 min, by which time the peak developed force had reached a steady state. Two groups of preparations were studied. In the test group, cumulative doses of alfentanil (0.001–0.5 mM) were administered to the tissue bath at 10-min intervals. In the time-control group, equal volumes of distilled water (diluent for alfentanil) were added to the tissue bath at the same time intervals as those of the test group. The frequency of contraction of right atrial-sinoatrial node, peak developed force (F_o), time-to-peak developed force, maximum rate of rise and fall of the developed force ($+dF/dt_{max}$ or $-dF/dt_{max}$) as well as time-to-50% relaxation of peak developed force were analyzed.

At the end of each experiment, the length and weight of each papillary muscle were measured. The cross-sectional area of the papillary muscle was then calculated (weight/length), assuming a tissue density of 1.06 g/cm^3. Variables involving force of papillary muscle were corrected by the cross-sectional area. In each preparation, the results were expressed as a percentage of the baseline value (100%) immediately before administration of alfentanil or diluent. Differences between the alfentanil group and time-control results were analyzed by analysis of variance (10). Differences from the baseline value (100%) within a group were analyzed by the Scheffé F-test. A *P* value of <0.05 was considered to be statistically significant.

Materials

Alfentanil HCl was supplied by Janssen Pharmaceutica. Stocks of 0.1 M and 0.01 M alfentanil HCl were prepared in distilled water. For the test group, volumes of 5–200 µL from the appropriate alfentanil stock solutions were added cumulatively to a 50-mL tissue bath containing modified Krebs' solution. Equal volumes of distilled water were added for the time-control group. All chemicals were reagent grade and were prepared in distilled water.

Results

In all three muscle preparations there were no statistically significant differences in baseline values between time-control and alfentanil groups in any of the control variables measured during isometric contraction (Tables 1 and 2).

Effects of Alfentanil on the Frequency and Isometric Developed Force of Contraction in Isolated Right Atria

In time-control preparations there was no significant change in frequency of contraction from the 100% baseline value (Figure 1). Alfentanil (0.5 mM) significantly decreased the frequency of contraction from values at 0.001 mM and 0.01 mM and, in fact, stopped spontaneous contractions in three of seven preparations. Frequency of contraction values at 0.1 mM and 0.5 mM alfentanil were significantly decreased (16% and 52%, respectively) from time-control values. Maximum developed force tended to increase with increasing alfentanil concentrations, significantly differing from time-control values at 0.01 mM and 0.1 mM drug (increases of 7% and 20%, respectively) (Figure 2). The maximum rate of rise of developed force also tended to increase over comparable time-control values and differed significantly from them at 0.01 mM, 0.05 mM, and 0.1 mM

Table 1. Control Parameters of Contraction in Right and Left Atria

	Frequency (beats/min)	F_o (g)	$+dF/dt_{max}$ (g/s)	TPF (ms)	$-dF/dt_{max}$ (g/s)	$t_{50\% \, relax}$ (ms)
Right atrium						
Time control ($n = 6$)	116.3 ± 7.3	0.9 ± 0.2	18.0 ± 4.8	85.8 ± 3.7	13.4 ± 3.7	61.0 ± 2.9
Test ($n = 7$)	129.5 ± 8.1	1.4 ± 0.2	26.1 ± 4.8	87.1 ± 3.2	11.6 ± 2.2	62.1 ± 3.4
Statistics	NS	NS	NS	NS	NS	NS
Left atrium						
Time control ($n = 6$)		1.5 ± 0.3	32.2 ± 5.8	80.1 ± 1.8	15.6 ± 2.9	52.0 ± 3.4
Test ($n = 7$)		1.7 ± 0.5	36.9 ± 10.2	75.7 ± 1.7	16.3 ± 6.5	51.5 ± 4.3
Statistics		NS	NS	NS	NS	NS

Values are mean ± SEM.

n, number of preparations; Time control, no drug, for diluent study; Test, preparations for alfentanil study; Frequency, frequency of contraction; F_o, peak developed force; $+dF/dt_{max}$, maximum rate of rise of developed force; TPF, time-to-peak developed force; $-dF/dt_{max}$, maximum rate of fall of developed force; $t_{50\% \, relax}$, time-to-50% relaxation of peak developed force; NS, no statistically significant difference in variables between the time control and test groups by analysis of variance.

Table 2. Control Parameters of Contraction in Right Ventricular Papillary Muscle

	A (mm^2)	F_o (g)	T (g/mm^2)	$+dT/dt_{max}$ ($g \cdot s^{-1} \cdot mm^{-2}$)	TPF (ms)	$-dT/dt_{max}$ ($g \cdot s^{-1} \cdot mm^{-2}$)	$t_{50\% \, relax}$ (ms)
Time control ($n = 8$)	1.0 ± 0.1	0.4 ± 0.2	0.4 ± 0.1	2.4 ± 0.8	182.2 ± 13.3	2.5 ± 1.0	133.1 ± 5.3
Test ($n = 11$)	1.0 ± 0.1	0.6 ± 0.2	0.5 ± 0.1	3.1 ± 0.7	190.0 ± 11.0	1.7 ± 0.3	118.2 ± 7.1
Statistics	NS	NS	NS	NS	NS	NS	NS

Values are mean ± SEM.

n, number of preparations; Time control, no drug for diluent study; Test, preparations for alfentanil study; A, cross-sectional area; F_o, peak developed force; $T = F_o/A$, peak developed tension; $+dT/dt_{max}$, maximum rate of rise of developed tension; TPF, time-to-peak developed force; $-dT/dt_{max}$, maximum rate of fall of developed tension; $t_{50\% \, relax}$, time-to-50% relaxation of peak developed force; NS, no statistically significant difference in variables between the time controls and test groups by analysis of variance.

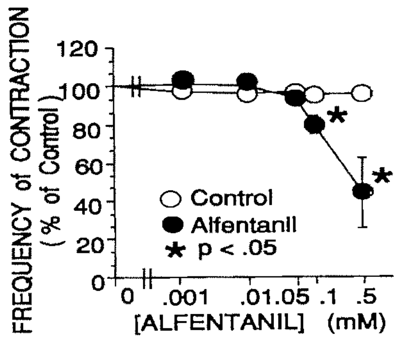

Figure 1. Cumulative dose-response relationship of alfentanil on the frequency of contraction of isolated spontaneously beating right atrial preparations, shown as percentage of baseline (100%) (% of control). Mean ± SEM. ○, No drug (time control) ($n = 6$); ●, alfentanil ($n = 7$). *$P < 0.05$ compared with the corresponding time-matched control.

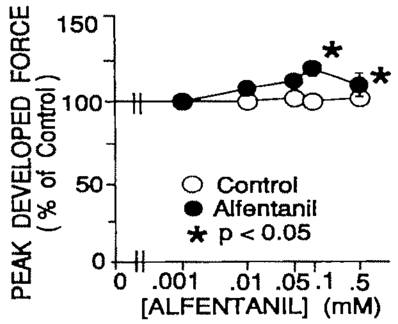

Figure 2. Cumulative dose-response relationship of alfentanil on the peak developed force in isolated right atrial preparations, shown as a percentage of baseline (100%) (% of control). Mean ± SEM. ○, No drug (time control) ($n = 7$); ●, alfentanil ($n = 7$). *$P < 0.05$ compared with the corresponding time-matched control.

alfentanil (up 15%, 21%, and 26%, respectively) (Table 3). Increases in the latter two variables did not change the time-to-peak developed force, which remained stable for both time-control and alfentanil preparations (Table 4). Maximum rate of fall of developed force and the time-to-50% relaxation of peak developed force alfentanil values also did not differ significantly from time-control values (Tables 5 and 6).

Effects of Alfentanil on Isometric Developed Force in Isolated Left Atria

In left atria, peak developed force and the maximum rate of both rise and fall of developed force increased dramatically and dose-dependently as alfentanil concentration increased to 0.1 mM and then to a lesser degree at 0.5 mM drug (Figures 3 and 4). Time-control values for the three variables also tended to increase with time (cumulative vehicle addition), but these increases did not differ significantly from the

Table 3. Effects of Alfentanil on the Maximum Rate of Rise of Developed Force ($+dF/dt_{max}$) (% of Baseline)

[Alfentanil] (mM)	Right atrium		Left atrium		Right ventricular papillary muscle	
	Time control ($n = 6$)	Alfentanil ($n = 7$)	Time control ($n = 6$)	Alfentanil ($n = 7$)	Time control ($n = 8$)	Alfentanil ($n = 11$)
0	100	100	100	100	100	100
0.001	100.3 ± 2.6	110.3 ± 4.4	102.3 ± 2.0	105.4 ± 2.6	98.2 ± 2.2	102.8 ± 4.7
0.01	101.0 ± 2.0	115.7 ± 4.2^a	106.8 ± 3.5	125.6 ± 5.7^a	94.5 ± 2.5	91.1 ± 3.4
0.05	100.8 ± 2.5	122.1 ± 6.2^a	108.3 ± 4.1	159.8 ± 10.3^a	96.2 ± 6.0	96.9 ± 6.8
0.1	100.5 ± 2.5	126.2 ± 7.1^a	109.4 ± 5.2	181.9 ± 15.7^a	96.0 ± 6.9	98.9 ± 9.1
0.5	102.9 ± 3.0	104.8 ± 8.9 ($n = 4$)	110.1 ± 5.9	170.8 ± 16.6^a	89.3 ± 4.8	66.6 ± 9.3

Values are mean ± SEM.

n, number of preparations; Time control, no drug, in the presence of cumulative volumes of the diluent; Alfentanil, in the presence of cumulative doses of alfentanil.

$^a P < 0.05$ compared with the corresponding time-matched controls by analysis of variance.

Table 4. Effects of Alfentanil on the Time-to-Peak Developed Force (% of Baseline)

[Alfentanil] (mM)	Right atrium		Left atrium		Right ventricular papillary muscle	
	Time control ($n = 6$)	Alfentanil ($n = 7$)	Time control ($n = 6$)	Alfentanil ($n = 7$)	Time control ($n = 8$)	Alfentanil ($n = 11$)
0	100	100	100	100	100	100
0.001	97.2 ± 2.4	97.3 ± 4.0	101.0 ± 0.6	94.9 ± 3.1	97.8 ± 1.3	95.1 ± 2.0
0.01	101.4 ± 0.6	99.1 ± 2.6	102.0 ± 1.0	96.4 ± 2.2^a	99.9 ± 2.9	101.6 ± 1.7
0.05	100.9 ± 0.6	99.4 ± 3.3	102.7 ± 1.6	98.7 ± 1.9	96.2 ± 1.5	103.8 ± 2.3^a
0.1	99.8 ± 2.1	100.4 ± 2.8	101.0 ± 1.7	98.4 ± 2.2	95.2 ± 2.0	100.2 ± 1.9
0.5	100.5 ± 1.8	106.3 ± 4.7 ($n = 4$)	102.7 ± 1.9	105.4 ± 4.5	94.8 ± 1.8	104.8 ± 2.2^a

Values are mean ± SEM.

Abbreviations are explained in Table 3.

$^a P < 0.05$ compared with the corresponding time-matched controls by analysis of variance.

Table 5. Effects of Alfentanil on the Maximum Rate of Fall of Developed Force ($-dF/dt_{max}$) (% of Baseline)

[Alfentanil] (mM)	Right atrium		Left atrium		Right ventricular papillary muscle	
	Time control ($n = 5$)	Alfentanil ($n = 5$)	Time control ($n = 5$)	Alfentanil ($n = 5$)	Time control ($n = 8$)	Alfentanil ($n = 11$)
0	100	100	100	100	100	100
0.001	112.4 ± 11.0	109.3 ± 9.2	93.3 ± 8.8	101.8 ± 4.8	101.8 ± 2.2	94.8 ± 3.6^a
0.01	101.9 ± 3.0	106.3 ± 3.4	96.4 ± 9.3	125.9 ± 5.8^a	97.4 ± 4.0	96.8 ± 7.7
0.05	103.0 ± 2.1	107.3 ± 6.3	97.4 ± 6.8	157.5 ± 14.2^a	86.4 ± 8.5	95.0 ± 7.3
0.1	103.8 ± 3.4	98.0 ± 13.2	111.0 ± 8.9	238.1 ± 58.4	96.0 ± 2.8	88.4 ± 13.4
0.5	99.8 ± 4.1	76.3 ± 22.8 ($n = 4$)	109.7 ± 10.0	158.1 ± 21.8	90.6 ± 4.1	54.8 ± 9.4^a

Values are mean ± SEM.

Abbreviations are explained in Table 3.

$^a P < 0.05$ compared with the corresponding time-matched controls by analysis of variance.

baseline values (100%). Alfentanil peak developed force at ≥0.05 mM was significantly higher than results obtained using ≤0.01 mM drug and differed significantly from time-control values. Maximum rate of rise of developed force values with alfentanil at ≥0.05 mM differed significantly from that at 0.001 mM. The drug group results were significantly higher than the time-control results at ≥0.01 mM (Table 3). Maximum rate of fall of developed force with alfentanil was increased significantly from time-control group values at 0.01 and 0.05 mM (Table 5). Both time-to-peak developed force (Table 4) and time-to-50% relaxation of peak developed force (Table 6) for left atria did not differ significantly between the time-control and the

Table 6. Effects of Alfentanil on the Time-to-50% Relaxation of Peak Developed Force ($t_{50\%\ relax}$) (% of Baseline)

[Alfentanil] (mM)	Right atrium		Left atrium		Right ventricular papillary muscle	
	Time control ($n = 5$)	Alfentanil ($n = 5$)	Time control ($n = 5$)	Alfentanil ($n = 5$)	Time control ($n = 8$)	Alfentanil ($n = 11$)
0	100	100	100	100	100	100
0.001	96.7 ± 3.2	97.4 ± 5.3	103.5 ± 2.1	100.9 ± 4.7	101.1 ± 5.6	97.7 ± 2.9
0.01	117.1 ± 20.8	103.6 ± 3.0	108.6 ± 5.4	100.7 ± 3.9	106.9 ± 3.6	96.4 ± 4.0
0.05	97.0 ± 7.5	103.7 ± 3.2	110.9 ± 5.4	109.4 ± 3.8	98.9 ± 3.2	109.2 ± 4.7
0.1	95.8 ± 2.5	105.1 ± 6.3	106.6 ± 4.3	109.7 ± 4.2	96.7 ± 5.3	115.4 ± 5.4[a]
0.5	98.6 ± 1.5	120.5 ± 13.1 ($n = 4$)	108.0 ± 6.0	113.0 ± 2.5	98.1 ± 4.3	124.2 ± 8.0[a]

Values are mean ± SEM.
Abbreviations are explained in Table 3.
[a] $P < 0.05$ compared with the corresponding time-matched controls by analysis of variance.

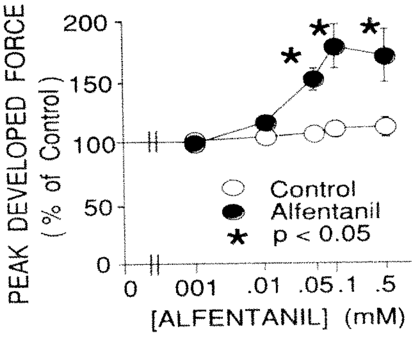

Figure 3. Cumulative dose-response relationship of alfentanil on the peak developed force in isolated left atrial preparations shown as percentage of baseline (100%) (% of control). Mean ± SEM. ○, No drug (time control) ($n = 6$); ●, alfentanil ($n = 7$). *$P < 0.05$ compared with the corresponding time-matched control.

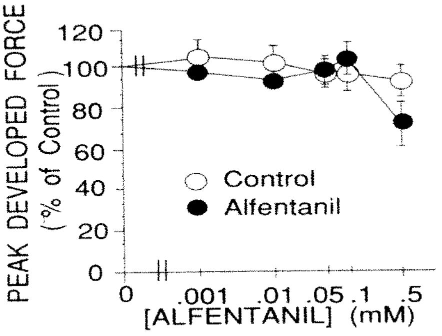

Figure 5. Cumulative dose-response relationship of alfentanil on the peak developed force in isolated papillary muscle preparations shown as percentage of baseline (100%) (% of control). Mean ± SEM. ○, No drug (time control) ($n = 8$); ●, alfentanil ($n = 11$).

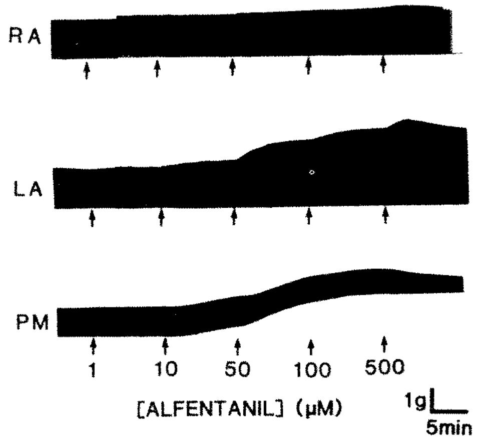

Figure 4. Tracings showing the effect of cumulative doses of alfentanil on the peak developed force and resting force of isometric contraction in isolated right atrium (RA), left atrium (LA), and papillary muscle (PM). *Arrow* = administration of alfentanil (1–500 μM = 0.001–0.5 mM); each of the tracings is representative of 3–5 preparations.

drug groups but the time-to-50% relaxation of peak developed force at 0.5 mM alfentanil was significantly higher than the ≤0.01 mM values.

Effects of Alfentanil on Isometric Developed Tension in Isolated Right Ventricular Papillary Muscle

There were no significant differences between time-control and alfentanil values for both peak developed tension (Figure 5) and maximum rate of rise of developed tension (Table 3); however, for each variable, the 0.5 mM alfentanil value was significantly lower than values for ≤0.1 mM drug. Maximum rate of fall of developed tension was significantly lower for drug values at 0.001 mM and 0.5 mM alfentanil than for time-control values (decreasing 7% and 36%, respectively) (Table 5). The 0.5 mM alfentanil value was significantly lower than those of all lower concentrations. The time-to-peak tension values (Table 4) were significantly higher for alfentanil concentrations of 0.05 and 0.5 mM than for time-control values. The time-to-50% relaxation of peak developed force values (Table 6) at ≥0.1 mM alfentanil were significantly increased over corresponding time-control values.

Effects of Alfentanil on the Resting Force of the Isolated Cardiac Tissues

Alfentanil as low as 0.01 mM consistently increased the resting force in isolated papillary muscle (up 1.91 ± 4.9 g [5]), but did not change that of isolated right and left atria (0.03 ± 0.03 g [3], 0.07 ± 0.07 g [3], respectively) (Figure 4).

Discussion

This study shows that alfentanil (≥0.05 mM) caused direct decreases in the frequency of contraction of right atria and increased isometric contraction of isolated right and left atria, but not of papillary muscle. Alfentanil increased the peak developed force and maximum rate of rise and fall of the developed force in left atria to a greater degree than in right atria. In papillary muscle, but not in atria, alfentanil increased time-to-peak developed force and resting force.

The lesser degree of increased isometric force in right atria and no increase in papillary muscle can be derived from other effects of alfentanil. Alfentanil at concentrations as low as 0.01 mM caused contracture in papillary muscle, but not in the atria, which resulted in incomplete relaxation of the twitch, and thus, less peak developed force for the following twitch. In the spontaneously beating right atria, the isometric force is dependent on frequency of contraction (for review see Reference 11). There are triphasic curves for the force-frequency relationship; in general, force increases with increasing frequency of stimulation above 1 Hz, reaching a plateau at about 2–3 Hz and then declining at >2–3 Hz. At low frequency (<1 Hz), force decreases, reaching a nadir at 0.1–0.2 Hz, then increases again at <0.2 Hz. Using this triphasic pattern, we could speculate that decrease in the frequency of contraction in right atria from approximately 2 Hz (baseline value) to 1 Hz (in the presence of alfentanil) would result in decreases in contractile force. This reduction in force due to the frequency-force relationship would counteract the positive inotropic effect of alfentanil on the atrial preparation. Thus, a smaller increase in the isometric force was observed in spontaneously beating right atria than in left atria paced at 1 Hz.

Analysis of isometric twitch suggests that the positive inotropic effect (increases in peak and maximum rate of rise of developed force) occurring in both atrial preparations is due to an increase in the intensity and not in the duration (no change in time-to-peak developed force and time-to-50% relaxation of peak developed force) of the active state. In contrast, in the ventricular papillary muscle, a trend of negative inotropic effects (decreases in rate of rise and fall of isometric force) is due to a decrease in the intensity and increase in duration (increases in time-to-peak developed force and time-to-50% relaxation peak developed force) of the active state.

Our current knowledge of the contractile process in the myocardium (for review see References 12 and 13) is described briefly: an action potential is generated by depolarization of plasma membrane. It travels through an invagination of the membrane (transverse tubule), which triggers release of calcium from the sarcoplasmic reticulum (SR). The increased cytoplasmic free calcium concentration from calcium influx and/or calcium release from the SR would bind to the regulatory protein (troponin C) resulting in an interaction of actin and myosin that can be demonstrated with force development or muscle shortening (12,13). The positive inotropic effect of alfentanil action on the isometric force of atria and the contracture of ventricular myocardium could be directly due to an increase in cytoplasmic free calcium concentration by increasing calcium influx through plasma membrane, and/or releasing calcium from the SR, and/or due to increased sensitivity of the contractile proteins to calcium. On the other hand, during relaxation, the increased maximum rate of fall of peak developed force could be due to increased calcium efflux, and/or calcium reuptake by the SR, and/or dissociation of calcium-troponin C binding. These speculations remain to be tested.

The decreased heart rate in both intact animal (3,14) and isolated spontaneously beating right atrial preparations suggests that both direct and reflex mechanisms are involved in this slowing. A direct depression of heart rate is also suggested in intact animal (3) because there is no time lapse between changes in heart rate and left ventricular pressure. In clinical practice, alfentanil concentration is lower than in the present study, which may account for little change in heart rate (15–18). However, in alfentanil anesthesia, bradycardia has been reported (for review see References 1 and 2). This bradycardia has been considered to be the result of chronic treatment with β-adrenergic blocking agents and the concomitant administration of nitrous oxide anesthesia.

The threshold concentration of alfentanil (0.01 mM) causing increases in twitch tension of left atria in this study is >50-fold higher than that of the highest therapeutic total plasma concentration of 1000 ng/mL (19). Based on 92% bound by plasma membrane (19), the free fraction would be 0.19 μM. Thus, 0.01 M alfentanil used in this study would be about 53-fold of 0.19 μM estimated plasma free fraction. However, there is a wide variability in protein binding of alfentanil (20). Thus, with bolus injection of alfentanil in the whole animal and human, the observed effects of alfentanil in this study may occur. In intact dogs (3), transient increased left and right atrial pressure is consistent with increased isometric twitch in isolated atrial preparations of this study. The increased resting tension in ventricular myocardium would result in increased left ventricular end diastolic pressure (14) at a given end diastolic volume. On the other hand, it is also possible that the greater alfentanil-induced increases in resting tension in ventricular myocardium than in atrial tissue are due to inefficient oxygen diffusion or increased oxygen consumption. This remains to be documented. The negative chronotropic effect with no change in contraction of ventricular myocardium in this study may result in decreases in cardiac output (3).

In summary, at high concentrations, alfentanil causes direct negative chronotropic and positive inotropic effects on the isolated right atrial-sinoatrial node and left atrium. Alfentanil produces contracture in the isolated papillary muscle but not in isolated atria of the rabbit.

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Negative Inotropic Effect of Ketamine in Rabbit Ventricular Muscle

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RUSY BF, AMUZU JK, BOSSCHER HA, REDON D, KOMAI H. Negative inotropic effect of ketamine in rabbit ventricular muscle. Anesth Analg 1990;71:275–8.

The effect of ketamine on myocardial contractile force was examined in rabbit papillary muscles in order to determine the underlying mechanism of action of the anesthetic. Ketamine HCl (20 and 40 mg/L) inhibited rested-state contractions that are dependent on the transsarcolemmal influx of Ca^{2+} for activation and reduced the upstroke velocity of the slow action potential, which reflects Ca^{2+} influx through the slow Ca^{2+} channel. On the other hand, ketamine had a relatively small effect on potentiated-state contractions and no effect on rapid cooling induced contractures, both of which are activated by the release of Ca^{2+} stored in the sarcoplasmic reticulum. These results suggest that ketamine inhibition of transsarcolemmal Ca^{2+} influx plays a major role in the negative inotropic action of the anesthetic.

Key Words: ANESTHETICS, INTRAVENOUS—ketamine. HEART, MYOCARDIAL FUNCTION—ketamine.

Ketamine exerts both negative (1–9) and positive (5,9–12) inotropic effects in isolated myocardial preparations. The positive inotropic effect involves endogenous catecholamine release in dog myocardial preparations (5,9) but not in rat myocardium (11,12). Rabbit ventricular muscle is particularly suited for the study of the negative inotropic effect of ketamine because only negative inotropy has been reported for ketamine in this tissue (1,8). In the present study we examined the effects of ketamine in isolated rabbit papillary muscles under conditions wherein the contractile activity depends predominantly either on the transsarcolemmal influx of Ca^{2+} or on the release of Ca^{2+} stored in the sarcoplasmic reticulum. Rested-state contractions in rabbit ventricular muscle are known to be activated by the transsarcolemmal influx of Ca^{2+}, as Ca^{2+} in the sarcoplasmic reticulum is largely depleted (13). The upstroke velocity of the slow action potential elicited in K^+-depolarized muscles in the presence of isoproterenol is a measure of transsarcolemmal Ca^{2+} influx through the slow Ca^{2+} channel (14). In contrast, potentiated-state contractions are activated predominantly by Ca^{2+} stored in and released from the sarcoplasmic reticulum (15,16). Finally, contractures induced by rapid cooling reflect the release of Ca^{2+} stored in the sarcoplasmic reticulum (17,18). It will be shown in the present study that ketamine inhibits the rested-state contraction and the upstroke velocity of the slow action potential, whereas it has relatively small effects on potentiated-state contractions and no effect on rapid-cooling induced contractures, suggesting that the anesthetic exerts its negative inotropic effect mainly by reducing the transsarcolemmal influx of Ca^{2+}.

Materials and Methods

Rabbits (weighing about 2 kg each) were anesthetized by intravenous injection of about 50 mg/kg of pentobarbital. Papillary muscles isolated from right ventricles were used. A total of 26 muscles with a diameter of 1.0 ± 0.3 mm (mean ± SD) were used in this study. Of these, eight were used to examine ketamine's effect on rested-state, potentiated-state, and steady-state contractions; six were used in the rapid cooling contracture experiments; and 12 muscles were used to examine the anesthetic's effect on the slow action potential. The muscles were mounted vertically in a tissue bath (45 mL) maintained at 30°C, except for the

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measurements of the slow action potential and rapid cooling induced contracture, for which the muscles were mounted horizontally in a 1-mL flow-through chamber. Isometric contractions, elicited at a muscle length of L_{max} (the length at which the developed force is maximal), were measured with a Statham UC-2 force transducer and recorded on a Gilson polygraph. These preparations were stable for the duration of experiments lasting 2–3 h. The standard medium used was a Krebs–Henseleit bicarbonate of the following composition: NaCl, 115 mM; KCl, 5.9 mM; $CaCl_2$, 2.5 mM; $MgCl_2$, 1.2 mM; NaH_2PO_4, 1.2 mM; Na_2SO_4, 1.2 mM; $NaHCO_3$, 25 mM; glucose, 5.6 mM; and ethylenediaminetetraacetic acid, 0.05 mM (added to chelate trace metals). A high-K^+ medium, used for measurement of the slow action potential, contained 26 mM KCl and correspondingly less NaCl to maintain the same ionic strength as the standard medium. Slow action potentials were elicited in the presence of 0.1 μM isoproterenol (14). Media were equilibrated with a gas mixture of 95% O_2 and 5% CO_2.

The muscles were stimulated with a pair of field electrodes (Ag/AgCl or Pt) using an American Electronics Laboratory or a Grass stimulator. Rectangular wave stimuli were 4 ms in duration with a voltage 50% above threshold. Rested-state contractions were elicited after 20 min of rest without stimulation. Slow action potentials were measured at a stimulation frequency of 0.1 Hz using standard glass microelectrodes containing 3 M KCl. These were amplified with a WPI model 773 electrometer and displayed and analyzed using a Norland 2001 programmable digital oscilloscope. The upstroke velocity was estimated from the rise time (from 10% to 90% depolarization), and the velocity reported in this paper is the average rather than maximum rate of rise of the slow action potential. Note that because it was seldom possible to maintain electrode impalement of the same cell throughout, the action potentials recorded in any given muscle in the absence and presence of the various concentrations of ketamine were obtained from different myocytes. Potentiated-state contractions were elicited after 2 s of rest following a 10-s train of stimulation at 2 Hz (19). Rapid cooling contractures were elicited by rapidly cooling the muscles to 3°C following a 5-s train of 2-Hz stimulation (20).

After baseline measurements, ketamine (as the hydrochloride) was added cumulatively, and the measurements were repeated 20 min after each addition of the anesthetic. Ketamine HCl was obtained from Parke-Davis. The effect of ketamine was statistically evaluated by repeated measure analysis of variance followed by Dunnett's t-test, except for the effect of ketamine on the upstroke velocity of slow action potentials, which was evaluated by unpaired t-test. The latter was considered appropriate because, as stated above, a different myocyte was involved in each measurement. $P < 0.05$ was considered to represent statistical significance.

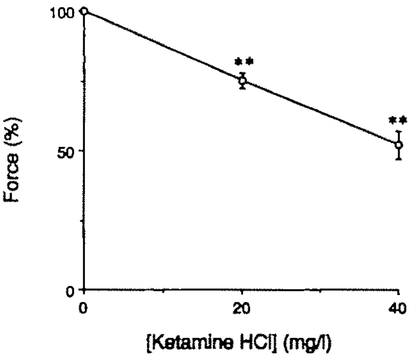

Figure 1. Effect of ketamine on rested-state contractions. Mean ± SEM (n = 8) of force expressed as percent of control. The control value (mean ± SEM, n = 8) was 0.31 ± 0.04 g/mm². **$P < 0.01$, compared with the control.

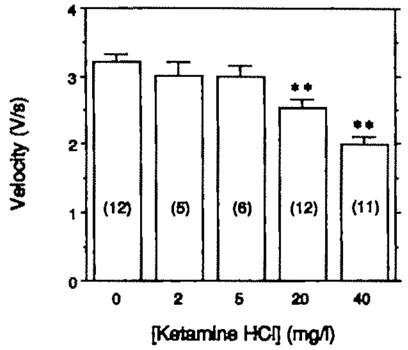

Figure 2. Effect of ketamine on upstroke velocity of the slow action potential. Mean ± SEM. Number of muscles are shown in parentheses. **$P < 0.01$, compared with the control.

This study was approved by the Animal Care and Use Committee of the University of Wisconsin, Madison.

Results

As seen in Figure 1, ketamine significantly inhibited the rested-state contraction. Figure 2 shows that ketamine at concentrations of 20 and 40 mg/L significantly reduced the upstroke velocity of the slow action potential, but had no significant effect at 2 and 5 mg/L. The effect of ketamine on the force of steady-state contraction at different stimulation frequencies (Figure 3) shows that ketamine significantly inhibited contractile force in the frequency range of 0.1–2.0 Hz.

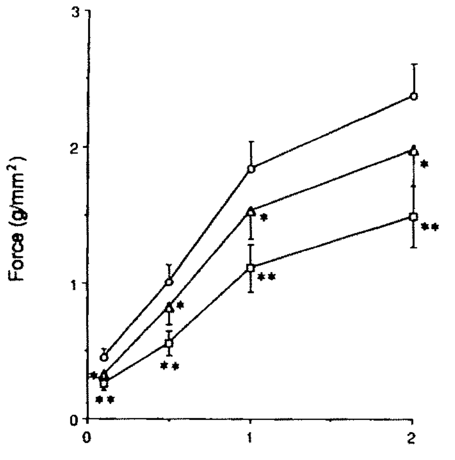

Figure 3. Effect of ketamine on steady-state contractions at different stimulation frequencies. Mean ± SEM ($n = 8$). ○, control; △, +20 mg/L ketamine HCl; □, +40 mg/L ketamine HCl. $^{*}P < 0.05$ and $^{**}P < 0.01$, compared with the corresponding control value.

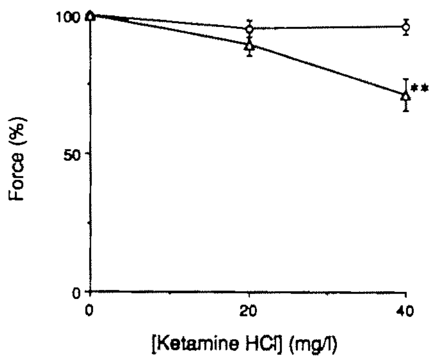

Figure 5. Effect of ketamine on potentiated-state contractions and rapid cooling contractures. ○, rapid cooling contractures, mean ± SEM ($n = 6$) of force expressed as percent of control. The control value (mean ± SEM, $n = 6$) was 1.20 ± 0.20 g/mm². △, potentiated-state contractions; mean ± SEM ($n = 8$) of force expressed as percent of control. The control value (mean ± SEM, $n = 8$) was 2.90 ± 0.30 g/mm². $^{**}P < 0.01$, compared with control.

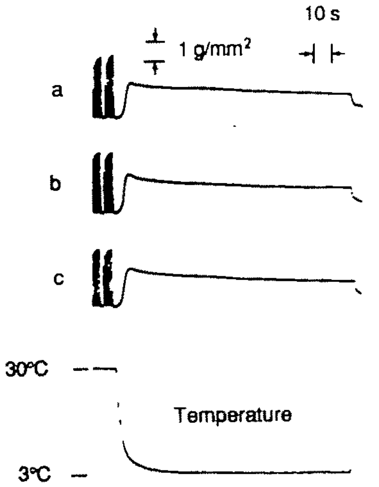

Figure 4. Effect of ketamine on rapid cooling contracture. Contracture was induced by rapid cooling of the muscle following a brief stimulation at 2 Hz (20). Traces are (from the top) (a), control; (b), +20 mg/L ketamine HCl; and (c), +40 mg/L ketamine HCl.

The force *increases* accompanying stimulation frequency increases from 0.1 to 0.5 Hz and 0.5 to 1.0 Hz were significantly ($P < 0.01$) reduced by 40 mg/L but not by 20 mg/L of ketamine. Figure 4 illustrates the experimental protocol used to measure the effect of ketamine on rapid cooling induced contractures. Ketamine had a small effect on potentiated-state contractions that was significant only for the high (40 mg/L) dose, whereas the anesthetic had no effect on rapid cooling induced contractures (Figure 5).

Discussion

The observed inhibition of the rested-state contraction and the reduction of the upstroke velocity of the slow action potential by ketamine suggests that the anesthetic reduces the transsarcolemmal influx of Ca^{2+} involved in the activation of contractile activity (13,14). In addition, a reduction of the force increase accompanying an increase in stimulation frequency, observed also by Davies and McCans (8), is consistent with an inhibition of Ca^{2+} influx by ketamine, because an increase in stimulation frequency is known to increase Ca^{2+} influx through the slow channel (16). It is very likely that a reduction in the transsarcolemmal influx of Ca^{2+} contributes to the negative inotropic effect of ketamine in rabbit papillary muscles, in which contractile activity is highly dependent on Ca^{2+} from this source. In cardiac muscle preparations such as rat ventricular muscles and atrial muscles of various species, the contractile activity is highly dependent on Ca^{2+} released from the sarcoplasmic reticulum (21,22). It should be noted that a positive inotropic effect of ketamine has been observed in those preparations (9,11,12), although a negative inotropic effect of the anesthetic in rat muscle has also been reported, albeit at a relatively high dose (2). In the present study, using rabbit papillary muscles, ketamine had only a negative inotropic effect. The anesthetic had a relatively small negative inotropic effect on the force of potentiated-state contractions and no effect on rapid cooling contractures, both of which are dependent on Ca^{2+} released from the sarcoplasmic reticulum but involve different Ca^{2+} release mechanisms. This suggests that in rabbit ventricular myocardium, ketamine does not significantly decrease the availability of sarcoplasmic reticular Ca^{2+} for the activation of contractile activity. It should be noted that Riou et al. (12) found that ketamine has a slight inhibitory effect on potentiated-state contractions in rat papillary muscles and *decreases* the rate of decay of the potentiated state. This is in contrast to the action of caffeine, which increases the rate of Ca^{2+} efflux from the sarcoplasmic reticulum and, consequently, increases the rate of decay of the potentiated state (15). In addition, although ketamine converts a positive staircase (force increase accompanying an increase in stimulation frequency) to a negative staircase (8), ryanodine, a specific inhibitor of sarcoplasmic reticular function, converts the negative staircase normally observed with rat myocardium to a positive one (23,24). Thus, it is apparent that the action of ketamine is not like that of typical inhibitors of sarcoplasmic reticular function.

In conclusion, the results of the present study suggest that ketamine inhibition of the transsarcolemmal influx of activator Ca^{2+} is an important mechanism underlying its negative inotropic effect in rabbit ventricular muscle, and that ketamine has relatively little effect on the availability of Ca^{2+} stored in and released from the sarcoplasmic reticulum in this preparation.

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Low-Flow Endobronchial Insufflation With Air for 2 Hours of Apnea Provides Ventilation Adequate for Survival

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MACKENZIE CF, BARNAS GM, SMALLEY J, MOORMAN R, BAPTISTE J. Low-flow endobronchial insufflation with air for 2 hours of apnea provides ventilation adequate for survival. Anesth Analg 1990;71:279–84.

We tested the efficacy of low-flow endobronchial insufflation (EI) with air, as it may be useful in emergency situations in which positive-pressure mechanical ventilation is not possible. The only equipment required is a source of compressed air with flow controller and a specially designed insufflation catheter. The insufflation catheter has forked ends that can be positioned blindly in the mainstem bronchi. In six anesthetized, apneic dogs averaging 9.6 kg, we determined that the average air flow needed to maintain Pa_{O_2} *above 45 mm Hg and* Pa_{CO_2} *below 65 mm Hg after 30 min was 2.5 L/min. At these flow rates, all dogs survived 2 h of endobronchial insufflation with no neurologic dysfunction. The small internal diameters (0.8 mm) of the catheter ends increase gas exit velocity and allow for adequate oxygenation and* CO_2 *removal at low flow rates. Endobronchial insufflation could also be employed with cricothyroidotomy and a compressor for emergency situations in the field involving mass casualties, where oxygen supplies and equipment are limited.*

Key Words: VENTILATION, ENDOBRONCHIAL INSUFFLATION. VENTILATION, APNEIC. ANESTHETIC TECHNIQUES, ENDOBRONCHIAL.

Continuous flow ventilation techniques produce stationary lungs, rib cage, diaphragm, and abdomen; this may be particularly desirable in certain types of surgery or radiological procedures. The continuous flow techniques include apneic oxygenation (1–3), tracheal insufflation of oxygen (4), and endobronchial insufflation (EI) of air or oxygen (5–12). Unlike tracheal insufflation (5–11) techniques, EI is effective in removing carbon dioxide and can maintain normocarbia for several hours of apnea.

The use of very low flow EI would be beneficial when oxygen or air supplies and ventilatory equipment are limited, as in the case of mass casualties caused by inhalation of toxic materials that produce respiratory arrest or failure, including organophosphorus poisons (13) or methylisocyanate (14). Moreover, use of minimum flows for EI is relevant to EI use during nonemergency clinical situations in view of disadvantages of high flows that include mucosal damage (15), pneumothorax (16), elevation of alveolar pressure with a decrease in arterial pressure (17), and cooling (8).

This study determines the efficacy of low-flow EI using small catheters in ideal circumstances. Modifications of this prototype may be potentially useful in a field situation, where conventional mechanical ventilators are unavailable or where their use may not be feasible. In such situations, simplicity of equipment, ease of subject preparation, and limitations in the supply of oxygen and fresh gas supply may be vital concerns. All that is needed in the technique we describe is a high-pressure source of room air (a compressor or compressed air tank with flow controller), a specially designed insufflation catheter, and access to the airway.

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Methods

Six beagle dogs averaging 9.6 kg (±0.4 SE) were anesthetized with 30 mg/kg intravenous pentobarbital after the study was approved by the institutional animal investigation committee. The trachea was intubated with a catheter to be used for EI (Sheridan Catheter Corp., Argyle, N.Y.) that was placed outside a Hi-Lo jet endotracheal tube with a 9.0-mm inner diameter (Mallinckrodt, Glens Falls, N.Y.). The EI catheter was made of 35-cm-long (1-mm inner diameter [ID], 1.9-mm outer diameter [OD]), single-lumen, stiff plastic tubing with a forked end composed of two flexible 3-cm-long prongs (0.8 mm ID, 1.5 mm OD). The prongs formed a 50° angle when unrestrained, but could be held together for placement through the larynx or through a 4-mm ID cricothyroidotomy cannula. Positioning of the prongs astride the carina was performed blindly and subsequently checked by bronchoscopy. We found that, in this study and in 20 other animals studied, slight adjustment of the tips was needed in about 20% of the dogs after initial blind placement to ensure optimal delivery of gas into the mainstem bronchi. After a 2-mg bolus of pancuronium bromide, thiamylal ($3\ mg{\cdot}kg^{-1}{\cdot}h^{-1}$) and pancuronium ($0.1\ mg{\cdot}kg^{-1}{\cdot}h^{-1}$) in 60 mL/h of normal saline were continuously infused for anesthesia and fluid maintenance. The lungs were ventilated with room air (Engstrom ER 312, Bromma, Sweden) at a rate of 12 breaths/min and tidal volume sufficient to maintain arterial CO_2 tension between 32 and 37 mm Hg. Body temperature was measured in the pulmonary artery and kept between 36.5 and 37.4°C with a heat lamp.

Systemic and pulmonary arterial pressures (Part and Ppa, respectively), airway pressure (Paw; monitored through a lumen in the wall of the endotracheal tube), and esophageal pressure (Pes; from a balloon [Mallinckrodt, Glens Falls, N.Y.] placed in the lower third of the esophagus) were monitored by pressure transducers (P231D Statham, Oxnard, Calif.). Arterial (Sao_2) and mixed venous ($S\bar{v}o_2$) oxygen saturations were continuously monitored by a pulse oximeter (Nellcor, Hayward, Calif.) placed on the tongue and by fiberoptic oximetry in the pulmonary artery (Oximetrics Abbott, Chicago, Ill.), respectively. Electrocardiograph, Part, Ppa, Paw, Pes, and Sao_2 were recorded continuously on an eight-channel ink jet recorder (Mingograf, Siemens-Elema, Sweden). Full sets of measurements, made serially throughout the experiments, also included measurements of arterial and mixed venous blood gas tensions and pH (blood sample simultaneously obtained and analyzed with temperature correction; Instrumentation Laboratories 713, Lexington, Mass.), and cardiac output measured by thermodilution. Blood samples were also analyzed for oxygen saturation (OSM_2, Radiometer, Copenhagen, Denmark).

The first full set of measurements were made during conventional mechanical ventilation, after all variables had achieved a steady state. Endobronchial insufflation was then started with humidified, heated compressed air at a constant flow rate. If Pao_2 was between 45 and 55 mm Hg and $Paco_2$ was between 55 and 65 mm Hg at the end of 30 min, the EI was continued for 1.5 additional hours; full sets of measurements were made 10, 20, and 30 min after the start of EI and at 15-min intervals thereafter. If the criteria were not met, conventional endotracheal mechanical ventilation was initiated to restore baseline variables, and EI at a lower or higher flow was started. We found that flows that led to Pao_2 lower than 45 mm Hg or $Paco_2$ higher than 65 mm Hg before 30 min were subsequently associated with rapid decreases in Sao_2 and $S\bar{v}o_2$ and deterioration in cardiovascular function. We therefore used these values of Pao_2 and $Paco_2$ as our definition of minimum adequate ventilation and continuously monitored oxygen saturation and intermittently measured blood gas tensions to gauge if EI needed to be discontinued and conventional ventilation initiated. For safety, to identify possible outflow obstruction during each period of EI, we also monitored Paw, which always remained near 0. Monitoring Pes confirmed lack of changes in lung volume and spontaneous breaths.

At the end of 2 h of successful EI, dogs were ventilated with room air using conventional ventilation and the anesthesia was discontinued. Neuromuscular block was reversed, when necessary, and the animals extubated when able to protect their airway. Clinical examination was carried out later the same day and on the following day to determine if neurologic dysfunction resulted from EI with minimum Pao_2 levels that averaged 51 mm Hg; the neurologic examination included assessment of gait, mental status, postural reactions, spinal reflexes, and cranial nerves.

A paired *t*-test with Bonferroni correction was used to compare corresponding variables at each time. The acceptable level of significance was 5%.

Results

Minimum flows ($\dot{V}_{min}$) of compressed air EI that produced Pao_2 levels between 45 and 55 mm Hg and $Paco_2$ levels between 55 and 65 mm Hg at 30 min ranged from 1.9 to 3 L/min (0.2 or 0.3 $L{\cdot}kg^{-1}{\cdot}min^{-1}$) (Table 1). The minimum Pao_2 and maximum $Paco_2$ levels achieved during the 2 h of $\dot{V}_{min}$ EI varied from 38 to 62 mm Hg and from 61 to 80 mm Hg, respectively.

Table 1. Ventilatory Variables During Conventional Mechanical Ventilation (CMV) and During 120 Min of Endobronchial Insufflation (EI) With Room Air

Dog No.	Weight (kg)	CMV $\dot{V}$ ($L \cdot kg^{-1} \cdot min^{-1}$)	EI $\dot{V}_{min}$ ($L \cdot kg^{-1} \cdot min^{-1}$)	CMV Pa_{O_2} (mm Hg)	CMV Pa_{CO_2} (mm Hg)	Min-EI Pa_{O_2} (t) [mm Hg (min)]	Max-EI Pa_{CO_2} (t) [mm Hg (min)]
1	10.5	0.4	0.2	111	36	51 (90)	72 (105)
2	9.5	0.3	0.2	107	34	60 (105)	65 (105)
3	8.0	0.4	0.3	107	36	62 (105)	61 (120)
4	9.5	0.3	0.3	103	37	56 (120)	68 (120)
5	10.0	0.3	0.3	97	34	43 (90)	71 (90)
6	10.0	0.3	0.3	109	32	38 (120)	80 (120)
Mean	9.6	0.33	0.27	106	35	51 (105)	69 (110)
±SE	0.4	0.02	0.02	5	1	4 (6)	3 (5)

$\dot{V}$, delivered minute ventilation during CMV; $\dot{V}_{min}$, minimum EI flows compatible with $Pa_{O_2} > 45$ mm Hg and $Pa_{CO_2} < 65$ mm Hg after 30 min; Min-EI Pa_{O_2}, minimum value for Pa_{O_2} during EI (the time after onset of EI that it occurred, *t*, is in parentheses); Max-EI Pa_{CO_2}, maximum value for Pa_{CO_2} during EI (time after onset in parentheses).

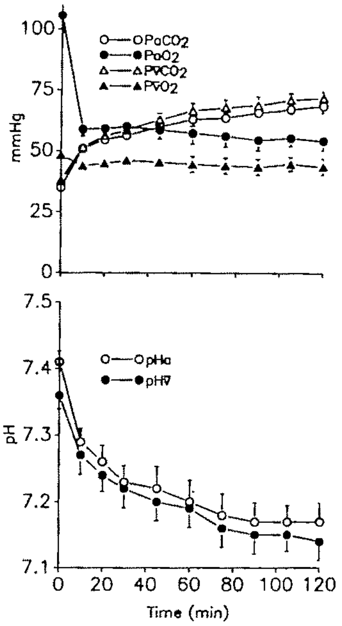

Figure 1. Average blood gas variables of six anesthetized, paralyzed dogs during conventional ventilation (time = 0) and 2 h of endobronchial insufflation at 0.2 or 0.3 $L \cdot kg^{-1} \cdot min^{-1}$. Standard error, where larger than symbol, is indicated by vertical bars. See text for statistical differences.

Blood gas tensions and pH during conventional ventilation and EI are shown in Figure 1; other cardiorespiratory variables are shown in Figure 2. As shown in Figure 1, upper graph, Pa_{CO_2} and $P\bar{v}_{CO_2}$ (mean ± SE mm Hg) increased ($P < 0.05$) from 35 ± 0.8 and 38 ± 0.8 on conventional ventilation to 51 ± 1.6 and 51 ± 2.5 after 10 min EI, respectively ($P < 0.05$). Pa_{O_2} (mean ± SE mm Hg) fell from 106 ± 2.0 to 59 ± 2.7 ($P < 0.05$); $P\bar{v}_{O_2}$ did not change. During the remaining 110 min, Pa_{CO_2} and $P\bar{v}_{CO_2}$ increased at a rate of about 0.2 mm Hg/min, while Pa_{O_2} and $P\bar{v}_{O_2}$ remained constant. In the first 10 min of EI, pHa (Figure 1, lower graph) decreased from 7.41 ± 0.02 to 7.29 ± 0.02 and pHv from 7.36 ± 0.02 to 7.27 ± 0.03 ($P < 0.05$). Both pHa and pHv decreased with further EI. After 90 min EI, arterial and mixed venous P_{O_2}, P_{CO_2}, S_{O_2}, and pH had not changed ($P > 0.05$). Sa_{O_2} and $S\bar{v}_{O_2}$ (Figure 2, upper left), measured from blood samples, both decreased after 10 min EI ($P < 0.05$) and then continued to decrease more slowly as EI continued.

During EI, Part (Figure 2, lower left) was greater than during conventional ventilation ($P < 0.05$). Systemic arterial pressure tended to increase throughout EI: values at 105 and 120 min were greater ($P < 0.05$) than at 75 min and the value at 120 min was also greater than at 90 min ($P < 0.05$). Pulmonary arterial pressure remained unchanged from levels associated with conventional ventilation until 105 min EI, when it increased ($P < 0.05$); it also increased further between 105 and 120 min ($P < 0.05$). Cardiac index (Figure 2, upper middle) increased with onset of EI and remained elevated above baseline values throughout the 2 h of EI ($P < 0.05$). Heart rate decreased between 60 and 75 min after EI began ($P < 0.05$), but was otherwise unchanged (Figure 2, lower middle). Oxygen consumption ($\dot{V}_{O_2}$) (Figure 2, upper right) and O_2 delivery (Figure 2, lower right) calculated as cardiac index × arterial O_2 content (Ca_{O_2}) were unchanged ($P > 0.05$) during EI or compared with conventional mechanical ventilation values.

All animals awakened after neuromuscular blockade was allowed to wear off or was reversed. By the next morning all dogs were awake, standing, and taking fluids orally, and appeared normal on neurologic examination.

Discussion

Other continuous flow ventilation techniques, such as apneic oxygenation and tracheal insufflation of oxygen, require supplies of oxygen that negate their

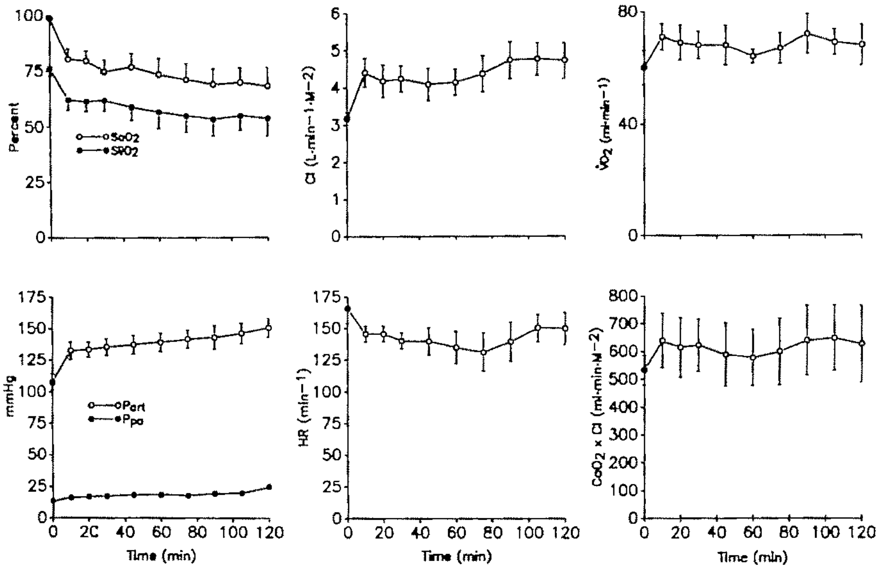

Figure 2. Cardiovascular variables (systemic [Part] and pulmonary arterial [Ppa] pressures; heart rate [HR]; and cardiac index [CI]), together with O_2 saturation (Sao_2 and $S\bar{v}o_2$), delivery ($Cao_2 \times CI$), and consumption ($\dot{V}o_2$) of six dogs during conventional ventilation (time = 0) and 2 h of endobronchial insufflation at 0.2 or 0.3 $L{\cdot}kg^{-1}{\cdot}min^{-1}$. Standard error, where larger than symbol, is indicated by vertical bars. See text for statistical differences and symbol definitions.

usefulness in many emergency situations. Additionally, the extremely high blood CO_2 levels found with those techniques (1–4) compromise acid-base balance and may cause cardiovascular depression (4).

Various approaches have been tried to reduce the flow rate needed for effective EI, including determination of optimum positioning and diameters of the EI catheter (11,18) and use of a relatively dense gas in combination with O_2 for insufflation (10,19). $\dot{V}_{min}$ in our studies of 0.2–0.3 $L{\cdot}kg^{-1}{\cdot}min^{-1}$ was less, on a $L{\cdot}kg^{-1}{\cdot}min^{-1}$ basis, than in other EI techniques using air at low flow (6,8). Other investigators (6) found that room air EI flow of about 0.5 $L{\cdot}kg^{-1}{\cdot}min^{-1}$, the lowest they tested, produced Pao_2 higher than 45 mm Hg in only one of four dogs, and in three other dogs they needed to add 50%–100% oxygen to ensure adequate oxygenation. $Paco_2$ at that flow rate was lower than 65 mm Hg in only three of seven dogs. The tips of their insufflation catheters were positioned 1.0–1.3 cm into each mainstem bronchus beyond the carina. It was subsequently shown that optimum CO_2 removal in dogs occurred when the point of entry of the insufflated gas was between 3.0 and 3.5 cm beyond the carina (18). Other investigators, who, like us, placed their catheters in that position found their $\dot{V}_{min}$ was 0.4 $L{\cdot}kg^{-1}{\cdot}min^{-1}$ and produced 52 mm Hg Pao_2 and $Paco_2$ of 62 mm Hg after 30 min (8). It should also be pointed out that optimum EI flow may not be strictly related to body weight, because weight-independent factors such as airway geometry are involved. In one study there was no relationship found between body weight and EI flow needed to maintain normocapnia in nine dogs (6). Our dogs were, on average, less than one-half the body weight of the dogs used in other studies (6,8). Our $\dot{V}_{min}$, averaging 2.5 L/min, was much less than half the flows in L/min used in those studies. Our lower $\dot{V}_{min}$ could be attributed to the fact that the inner diameters of our catheters (0.8 mm) were smaller than those used by other investigators. Decreasing the catheter diameter has the same effect on turbulence generated at the catheter exit as increasing the flow rate (20).

A marking line along the length of the catheter provides orientation, and the stiffness of the catheter is sufficient to allow use of torque to rotate the catheter within the trachea and to prevent catheter tip movement during EI. The forks open naturally astride the carina and, as described earlier, were successfully placed blindly without adjustment about 80% of the time. In field use, technicians trained to perform cricothyroidotomy could provide a route for insertion of the catheters. Our EI catheters pass easily through a cricothyroidotomy cannula (Portex minitracheostomy, Hythe, England) that has a 4-mm inner diameter, 5.4-mm outer diameter, and is 11.5 cm long, and can rapidly be placed percutaneously (21). Other investigators have found that 29 previously inexperienced technicians had a 83% first-time success rate at cricothyroidotomy after 1.5 h of training (22). With modification of our equipment, many subjects could be ventilated using the same source of air because the high impedance of such sources ensures that differences in subjects' airway resistance and respiratory system compliance will not affect distribution of flow among the subjects. The high pressure in the catheters decreases the possibility of clogging of one or both forks with airway secretions.

The present data suggest that the period of $\dot{V}_{min}$ EI ventilation may be extended for more than 2 h because, except for Part and Ppa, blood gas and cardiovascular variables remain stable after 90 min. The cardiovascular changes seen including the increase in cardiac index and intravascular pressures may be related to the hypercapnia. The decrease in heart rate appeared to be a baroreceptor reflex in response to the increases in systemic blood pressure. There were no changes in O_2 delivery or $\dot{V}O_2$ during EI, suggesting that a steady state was achieved without delivery-dependent $\dot{V}O_2$. In an emergency situation, how long low-flow EI will be compatible with survival depends on many factors, including the time-course and the degree to which spontaneous breathing returns. It is difficult to predict whether other room-air, low-flow EI techniques are compatible with survival after 2 h because the period of EI ventilation was only 15 min (6) or 30 min (8) in the other studies, and these investigators' animals were not awakened and examined.

We heated and humidified the compressed air used for EI. This was necessary because to determine $\dot{V}_{min}$, each dog needed to be exposed to more than one period of EI. Heating and humidification may minimize the complications arising from mucosal damage during EI, and we wanted to prevent these complications. We have not tested whether unhumidified gas at room temperature has adverse effects during our EI technique. However, we feel that with the low flows used, any adverse effects would be enormously outweighed by the advantages in our technique that maximize chances of survival. In addition, the technique of $\dot{V}_{min}$ was examined in ideal circumstances, and we have not determined its efficacy in pathological states. However, preliminary results of evaluation of high-flow EI in the presence of oleic acid pulmonary injury suggest that EI is effective even when pulmonary edema impairs gas exchange (23).

It is difficult to extrapolate, from our results, the flows compatible with survival in human subjects under similar conditions because, as well as scaling factors for body size, the differences in canine and human airway geometries must be considered. In clinical experiments, where 50%–100% oxygen was used for EI, flows needed to maintain adequate oxygenation ranged between about 0.5 $L \cdot kg^{-1} \cdot min^{-1}$ (7,17) and 1.6 $L \cdot kg^{-1} \cdot min^{-1}$ (16). $Pa{CO_2}$ levels ranged from 55 to 69 mm Hg after 8–30 min of EI. However, no study has used the types of catheter and bronchial positioning of catheters that we used in our present study. It is probable that a clinical EI technique similar to ours could be developed that will need lower flows than heretofore applied.

In conclusion, we have demonstrated a prototype ventilatory technique that may have a place for emergency use in the field, where other techniques may not be useful or available. Low-flow EI with air may be the only alternative in some situations to maintain ventilation until more comprehensive life-support equipment is obtained.

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ANESTH ANALG 285
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Doxacurium and Mivacurium Do Not Trigger Malignant Hyperthermia in Susceptible Swine

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SUFIT RL, KREUL JF, BELLAY YM, HELMER P, BRUNSON DB, WILL J. Doxacurium and mivacurium do not trigger malignant hyperthermia in susceptible swine. Anesth Analg 1990;71:285–7.

The role of succinylcholine in the precipitation of malignant hyperthermia (MH) necessitates the testing of new neuromuscular relaxants for their ability to trigger MH in MH-susceptible swine before general human use. We tested doxacurium and mivacurium, two new nondepolarizing bis-benzylisoquinolinium neuromuscular relaxants, at ED_{95} and at four times ED_{95} doses in swine previously documented to be MH-susceptible. In none of the 16 animals was MH triggered after administration of these relaxants, whereas all animals developed fatal MH after administration of halothane or halothane plus succinylcholine. Muscle biopsy specimens taken before administration of the relaxant confirmed that all animals had increased sensitivity to halothane, caffeine, or both. Thus, we conclude that doxacurium and mivacurium are not triggering agents of malignant hyperthermia in MH-susceptible swine.

Key Words: NEUROMUSCULAR RELAXANTS, DOXACURIUM, MIVACURIUM. ANESTHETICS, VOLATILE—halothane. HYPERTHERMIA, MALIGNANT.

Of concern in the search for better neuromuscular relaxants is the possibility that they, like succinylcholine, might trigger malignant hyperthermia (MH). Two new *bis*-benzylisoquinolinium agents, long-acting doxacurium chloride (BW A938U) and short-acting mivacurium chloride (BW B1090U), have been introduced for clinical use, but their safety with regard to MH remains unknown because they have not been tested for triggering potential. Recent introductions of the nondepolarizing relaxants vecuronium and atracurium have been coupled with testing in MH-susceptible swine that have "cleared" them of triggering potential (1,2). We have undertaken similar studies of doxacurium and mivacurium for the same purpose.

Methods

Animal Selection

Previously tested female Pietrain swine were obtained from the University of Minnesota College of Agriculture. All animals had been identified as MH-susceptible using a prescreening barnyard halothane exposure test (3,4). They were brought to the University of Wisconsin Veterinary Science facility for testing. They were at least 5 mo old, and there was no difference in age between groups. Their weights ranged from 67 to 165 kg with an average of 113 kg. At least 2 mo had elapsed since their exposure to halothane. The protocol followed was approved by the University's Animal Care Committee.

Procedure

Based on previous work in other test animals, ED_{95} doses (muscle tension less than 5% of initial maximal

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Received from the Departments of Neurology and Anesthesiology, School of Medicine, University of Wisconsin-Madison; the Department of Veterinary Science, School of Agriculture and Life Sciences, University of Wisconsin-Madison; and the Department of Medicine and Surgery, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, Wisconsin. Accepted for publication May 24, 1990.

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tension) were estimated to be about 0.01 mg/kg for doxacurium and 0.02–0.04 mg/kg for mivacurium (5,6). Beginning with those values in four swine used exclusively for the purpose of establishing the ED_{95} in swine, we incrementally changed the dose until we established the appropriate milligram per kilogram dose for each relaxant as measured by ulnar nerve-stimulated forefoot flexion. Sixteen other test animals were then randomly divided into four groups of four animals each. One group received doxacurium and a second group mivacurium at the previously determined ED_{95} dose. Two further groups, one for each drug, were given four times the ED_{95}. The animals were anesthetized with 10 mg/kg intravenous pentobarbital delivered through a marginal ear vein with anesthesia maintained by intermittent doses as needed. Tracheal intubation was accomplished without use of neuromuscular relaxants, with ventilation using O_2-N_2O ($FIO_2 = 0.4$) then initiated at a rate and volume to assure a PCO_2 of approximately 40 mm Hg. The external jugular vein was cannulated to obtain blood samples for measurement of levels of glucose, lactate, potassium, and ionized and total calcium. The superficial femoral or external carotid artery was cannulated to measure blood pressure and obtain blood samples for measurement of gas tensions. Venous pressures were not measured. End-tidal PCO_2 was monitored with a calibrated infrared gas analyzer. Temperature was monitored in the biceps femoris and rectum. The forefoot was immobilized, a pair of stimulating electrodes firmly fixed over the ulnar nerve, and the second or third digit wired through the hoof to a strain gauge whose output was recorded throughout the experiment. The nerve was stimulated supramaximally every 10 s with a Grass S44 stimulator.

To confirm MH susceptibility for each of the 16 animals, a trapezius muscle biopsy was performed for immediate in vitro testing for MH sensitivity. The data obtained with the following method were compared with control data from swine that were not MH-susceptible. Multiple muscle strips were placed in separate water baths and exposed to halothane of increasing concentration from 0.5%, 1.0%, 1.5%, 2.0%, and 3.0%, with the duration of each exposure being 5 min. We used a similar paradigm for caffeine in the absence of halothane at increasing concentrations from 0.125 to 0.25, 0.5, 1.0, 2.0, 4.0, and 8.0 mM for 3 min each. Some strips were exposed to 12.0, 16.0, 20.0, and 24.0 mM as well.

After the muscle biopsy, the protocol continued with two baseline measurements of blood gas tensions and blood levels of glucose, lactate, potassium, and calcium. The two sets of measurements were separated by 7–10 min, after which the relaxant being tested was administered in the appropriate dose. Although the initial protocol called for reversal of relaxant effects after the twitch height returned to 50% of the initial tension using 0.6 mg atropine and 1.25–5.0 mg neostigmine administered intravenously, reversal was not found to be needed. The twitch height always returned to normal within minutes. A calibrated vaporizer was then introduced into the ventilatory circuit and 3%–5% halothane was added to the O_2 and N_2O mixture. If cardiovascular depression developed, the concentration of halothane was reduced to 2%. A hyperthermic response was diagnosed on the basis of increasing muscle rigidity, end-tidal $PCO_2 > 50$ mm Hg, an increase in rectal temperature of 2°C, or an arterial $pH < 6.8$. If MH failed to develop in 10 min, 1 mg/kg succinylcholine was given intravenously. If MH failed to develop after the succinylcholine, that animal and the results obtained in it were eliminated from the experiment and another animal was substituted. Blood samples were drawn every 5 min during the triggering phase.

Results

Drug Administration

After relaxant administration all animals developed the expected decrease in twitch tension. The mean ED_{95} for doxacurium was 0.027 mg/kg; for mivacurium it was 0.304 mg/kg. The four times ED_{95} doses produced total loss of twitch tension. At no time during the administration of the test relaxants did any animal show evidence of muscle rigidity, increased end-tidal PCO_2, or increased heart rate, the most sensitive indicators of MH when MH was triggered in these animals later in the protocol. There were no changes in core or muscle temperature, nor in blood pressure or blood levels of glucose, lactate, potassium, or ionized or total calcium.

Muscle Testing

Control and positive-trigger animals had previously been given to the in vitro laboratory as unknowns. In the current study all but one doxacurium-treated animal developed a halothane- or caffeine-induced contracture indicative of MH susceptibility. That animal showed poor twitches of all muscle bundles during in vitro stimulation and was considered to represent a technical failure in obtaining the surgical biopsy specimen. In addition, a single animal that did show a contracture on blind interpretation of the

Table 1. In Vitro Contracture Testing

Group	Concentration halothane (%) required to increase muscle tension >0.2 g	Caffeine-specific concentration[a] [Mean (range)]
Normal swine	Not seen at 0.5%, 1.0%, 2.0%, or 3.0%	9.68 mM (6.81–16.31 mM)
Doxacurium in MH swine	0.5%[b]	1.75 mM (0.91–6.81 mM)
Mivacurium in MH swine	0.5%[b]	1.40 (0.75–2.65 mM)

MH, malignant hyperthermia.
[a]See Reference 7.
[b]Lowest concentration of halothane used.

muscle biopsy had been independently eliminated from the study because of failure to trigger at the terminal stage. During muscle testing with 0.5% halothane, all the other seven doxacurium-treated animals showed in vitro contractures of their muscle strips greater than 0.2 g. With caffeine two of the seven showed a contracture of 1 g at 1 mM, and four of the seven at 2 mM, and six of the seven at 4 mM, with the remaining animal not showing a 1-g or greater increase until exposed to 8 mM caffeine. The caffeine-specific concentrations (7) were calculated from a caffeine versus tension curve using three points taken from the initial increase in tension and for doxacurium ranged from 0.91 to 6.81 mM. In the mivacurium-treated animals, the in vitro muscle strips of all eight exposed to 0.5% halothane increased in baseline tension 0.2 g or greater, and they increased to 1.1 g or greater with exposure to 1.0% halothane. In the presence of caffeine, muscle strips of two of the eight animals responded with a 1-g contracture at 1.0 mM, in six of the eight with 2.0 mM, and in all with 4 mM caffeine. The caffeine-specific concentrations were less than 2.65 mM. A summary is provided in Table 1.

Physiology and Serum Chemistry

The earliest indicator of an MH episode was a rapid increase in end-tidal $P\mathrm{co}_2$. In each animal end-tidal $P\mathrm{co}_2$ increased to at least 88 mm Hg. The average increase from the prehalothane sample was 82 ± 29 mm Hg ($P = 0.0000$). The heart rate increased in 13 of 16 animals. The average increase for all 16 was 39 ± 34 beats/min ($P = 0.0005$). Serum lactate levels also increased in the 15 animals in which it was measured with the minimum increase being 5.0 mmol/L and the average 13.8 ± 8.8 mmol/L ($P = 0.0001$).

Discussion

Two new nondepolarizing muscle relaxants, doxacurium and mivacurium, do not act as triggering agents for MH in MH-susceptible swine. Unlike succinylcholine, both are nondepolarizing neuromuscular relaxants and would not be expected to cause increased muscle tension (8). Neither clinical muscle spasm nor rigidity was observed with the strain gauge. This was true even at doses four times the ED_{95}. Test animals were clearly MH-susceptible by previous halothane exposure testing, by terminal triggering in our experimental protocol, and by in vitro muscle biopsy criteria. Thus, these neuromuscular relaxants appear to be potent and effective in swine, which is in accord with human data (9,10). Moreover, by themselves they exhibit no propensity to increase resting muscle tension or trigger MH.

We wish to thank Scott Hubbard-Van Stelle for expert technical assistance.

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1990;71:288–94

Special Article

The Wood Library-Museum's 1858 Edition of John Snow's *On Chloroform and Other Anaesthetics*

J. R. Maltby, MB, FFARCS, FRCPC, and B. J. Bamforth, MD

MALTBY JR, BAMFORTH BJ. The Wood Library-Museum's 1858 edition of John Snow's *On Chloroform and Other Anaesthetics*. Anesth Analg 1990;71:288–94.

The original 1858 edition of John Snow's On Chloroform and Other Anaesthetics, *from which came the Wood Library-Museum of Anesthesiology reprints in 1971 and 1989, was donated to the Wood Library-Museum by Ralph Waters of Madison, Wisconsin, in 1967. The book contains a message of appreciation to Waters, dated October 1937, with the signatures of J. Blomfield, Charles King, and R. R. Macintosh as representatives of anesthesiology in England. Correspondence exists in the archives of the University of Wisconsin-Madison between Macintosh, Professor of Anaesthetics in Oxford, and Waters, Associate Professor in Madison. This reveals that Waters, during his visit to England in 1936, inspired British anesthetists to discover more of Snow's early contributions to anesthesiology, even though Waters himself did not possess* On Chloroform and Other Anaesthetics. *King, a manufacturer of anesthetic equipment, found a copy in the hands of Blomfield, an anesthetist at St. George's Hospital, London, where John Snow had worked. It was this copy that they presented to Waters, and that was delivered to Waters by hand when Waters' resident, Ivan Taylor, returned from Oxford to Madison. Blomfield's ownership of the book, in addition to his position as president of the Association of Anaesthetists of Great Britain and Ireland, explains why the inscription is in his handwriting.*

Key Words: HISTORY, SNOW, JOHN—Wood Library-Museum of Anesthesiology.

John Snow wrote two of the earliest texts on anesthesia. *On the Inhalation of the Vapour of Ether* was published in 1847 and sold 126 copies. His much larger second book *On Chloroform and Other Anaesthetics* was published posthumously in 1858 and sold 418 copies (1). *On Chloroform and Other Anaesthetics* is valued by anesthesiologists not only for its historical interest but also for the remarkable amount of scientific information that Snow accumulated during the first decade of anesthesia. The rarity of the original edition of *On Chloroform and Other Anaesthetics* and the demand for copies of the book prompted the Wood Library-Museum of Anesthesiology to produce its first facsimile reprints in 1954. The only original possessed by the Wood Library-Museum was in poor condition, and the quality of reproduction was not good. The number of 1954 reprints is not recorded (personal communication from P. Sim, Wood Library-Museum of Anesthesiology, 1990).

Dr. Ralph Waters (1883–1979) was the first American anesthesiologist to hold a university-salaried academic appointment when he became, in 1927, Assistant Professor of Surgery in charge of anesthesia at the University of Wisconsin, Madison. Anesthesiologists from many countries came to learn from him, and many of them went on to become chairmen of academic departments (2). Waters retired in 1949, and in 1967 he donated his original 1858 edition of *On Chloroform and Other Anaesthetics* to the Wood Library-Museum. It was from this book, which was in good condition, that 1000 reprints were made in 1971 and in 1989. The inscription in the frontispiece (Figure 1) records that the book was given to Waters in 1937, by three people, "as a sign of their appreciation of his kindness to British anaesthetists visiting America, & of his work for anaesthetists there, this book is

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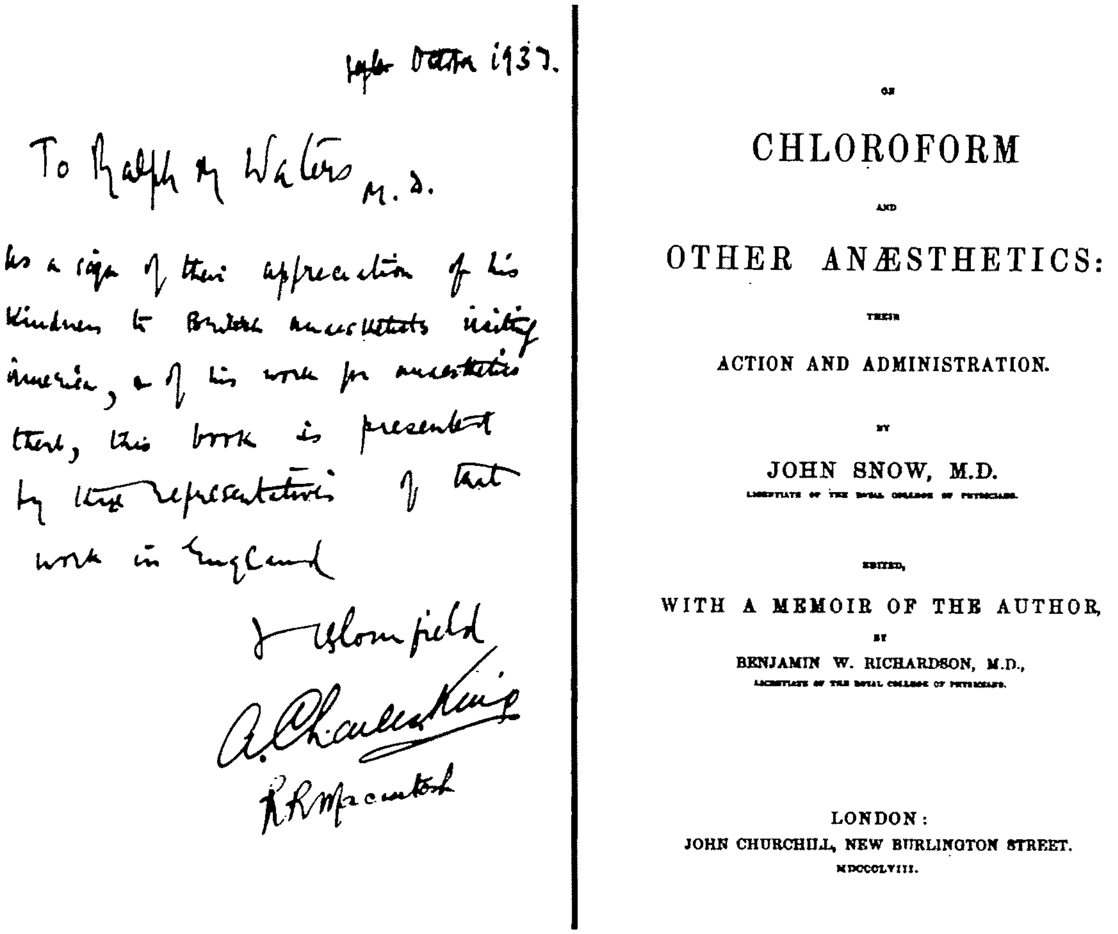


Sept October 1937.

To Ralph M Waters M.D.

As a sign of their appreciation of his kindness to British anaesthetists visiting America, & of his work for anaesthesia there, this book is presented by these representatives of that work in England

J Blomfield
A Charles King
R R Macintosh

ON

CHLOROFORM

AND

OTHER ANÆSTHETICS:

THEIR

ACTION AND ADMINISTRATION.

BY

JOHN SNOW, M.D.

EDITED,

WITH A MEMOIR OF THE AUTHOR,

BY

BENJAMIN W. RICHARDSON, M.D.,

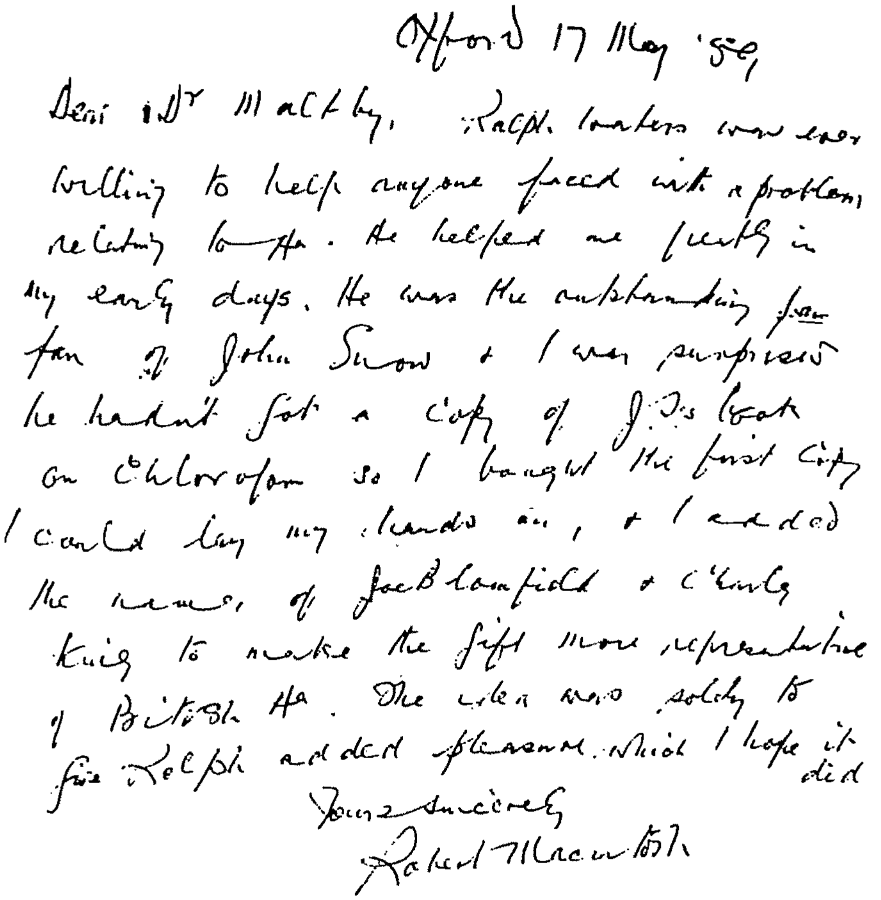
LONDON:
JOHN CHURCHILL, NEW BURLINGTON STREET.
MDCCCLVIII.

Figure 1. *Left*: Inscription to Ralph Waters. *Right*: Title page of the Wood Library-Museum's 1858 edition of John Snow's *On Chloroform and Other Anaesthetics*.

presented by these representatives of that work in England." The signatures are those of J. Blomfield, A. Charles King, and R. R. Macintosh. There are no records in the Wood Library-Museum concerning the significance of the three signatories, the ownership of the book before it was given to Waters, or the occasion on which it was presented.

Dr. Joseph Blomfield (1870–1948), the first signatory, was President of the Association of Anaesthetists of Great Britain and Ireland from 1935 to 1938 (3), and was editor of the *British Journal of Anaesthesia* from 1928 to 1948. Mr. A. Charles King, the second signatory, started a medical supply business in London after the First World War and subsequently specialized in the manufacture of anesthetic equipment. In 1949 he received the rare honor of being made an Honorary Fellow of the Section of Anaesthetics of the Royal Society of Medicine (4). The Charles King collection now forms the nucleus of a museum in the Association of Anaesthetists' headquarters in Bedford Square, London. Dr. Robert R. (later Sir Robert) Macintosh (1897–1989), the third signatory, was appointed to the Nuffield Chair of Anaesthetics at the University of Oxford in 1937 (5) and his subsequent influence on the development of our specialty was as widespread as that of Waters.

In May 1989 Sir Robert Macintosh, aged 91 and the only one of the four men named on the inscription who was still alive, recalled that the gift was his idea and that the other signatures were added to represent British anesthesiology (Figure 2). This was puzzling because, if the handwriting of the message (Figure 1) is compared with that of Macintosh's letter (Figure 2), it is clear that the message was written by Blomfield and that Macintosh merely signed it. This appeared to contradict Macintosh's memory of events of 50 years earlier. However, Blomfield was President of the Association of Anaesthetists in 1937, so it was possible that Macintosh invited him to write the message "to make the gift more representative of British Anaesthesia." Sir Robert's death in August 1989 (6) meant that further information concerning the



Oxford 17 May '89

Dear Dr Maltby, Ralph Waters was ever willing to help anyone faced with a problem relating to Ax. He helped me greatly in my early days. He was the outstanding ~~fan~~ fan of John Snow & I was surprised he hadn't got a copy of J.S.'s book on Chloroform so I bought the first copy I could lay my hands on, & I added the names of Joe Blomfield & Charles King to make the gift more representative of British Ax. The idea was solely to give Ralph added pleasure which I hope it did

Yours sincerely
Robert Macintosh

Figure 2. Letter from Sir Robert Macintosh, aged 91, giving his recollection of obtaining the book for Ralph Waters.

source of the book and its presentation had to be sought elsewhere. Records of Waters' visit to England, and those of Macintosh to the United States, during the 1930s were reviewed in the hope of finding a reference to the presentation of Snow's book.

Waters' Visit to Britain

In 1936 Waters was invited by the British Medical Association to be the guest speaker at their annual meeting in Oxford, and he combined this with a family holiday in England and Scotland, and a visit to Europe (7). He spent 1 month visiting various hospitals in London, and presented a paper before the Section of Anaesthetics of the Royal Society of Medicine of which he was made an honorary member. He also visited Charles King's anesthetic equipment showroom, and commented that the premises had become the mecca of the world's anesthetists. Noel Gillespie, a British anesthetist who emigrated in 1939 from London to Madison (2), wrote in 1954 (7): "British anaesthetists were unable to resist the spell of his [Waters'] simplicity, his friendliness, his keenness and his erudition. They had all heard, vaguely, of John Snow, but took him for granted. It remained for an American to arouse them to the fundamental importance of Snow's early contributions." Gillespie also stated that among Waters' most treasured possessions was the 1858 edition of Snow's *On Chloroform and Other Anaesthetics*, which was presented to him at the time of his visit to London. Waters visited London in 1936, so either Gillespie incorrectly assumed that the book was presented at that time or Blomfield's 1937 date on the inscription was wrong.

Sir Robert Macintosh's Visit to North America

Soon after Macintosh was appointed professor in the Nuffield Department of Anaesthetics in Oxford, he and other British anesthesiologists visited several centers in the United States and Canada. Madison, Wisconsin, was included in the tour, but Macintosh himself did not go there. He and his colleagues gave a report of this tour to the Royal Society of Medicine in London in March 1937 (8), 7 months before the date of the inscription, so the presentation could not have been made during that tour. It seemed unlikely that Macintosh would have made a second visit to the United States within a year, but inquiries at Oxford showed that one was indeed recorded in his travel diary (personal communication from J. Beinart Wellcome Unit for the History of Medicine, Oxford, 1989) and that it included Madison, but that the date was June 1937, not October.

The only other likely source of information was the University of Wisconsin, Madison, where Waters was working in 1937. It was there, in the Waters correspondence files, that a series of letters was found revealing the origin of the book, and explaining the apparent discrepancies concerning the date and the handwriting on the inscription.

Waters Correspondence Files

May 14, 1936—Macintosh to Waters

(Macintosh states that he cannot visit Madison on this trip.)

January 29, 1937—Rovenstine to Waters*

"When Macintosh was here, I mentioned Snow to him. He said immediately that, 'I will send you a copy [of *On Chloroform*] when I get back to England.' Evidently he tried to keep his word. Enclosed are some letters in evidence of his effort but not optimistic of success."

February 2, 1937—Waters to Rovenstine

"Macintosh's dealer, Lewis,† is very optimistic. I hope to goodness I can have an opportunity to buy one [1858 edition of Snow's book] for £2. 2s. They evidently have not looked into the matter very much. The book is being searched for by dealers everywhere without success. I found one German dealer who knew very well that it was rare and had been looking for it for years."

June 16, 1937—Waters to Rovenstine

"I must say that I have decided to go to the Ottawa meeting but go by train and be back as soon as possible, which should give me more time with Macintosh and be better for my accomplishments."

(Macintosh arrived in New York aboard the *Normandy* on June 19th, and joined Waters and others at the American Medical Association Meeting in Atlantic City, New Jersey. They drove back to Madison together.)

June 29, 1937—Macintosh to Waters

"I am grateful to you and yours for so much assistance. I somewhat selfishly chose the time of my visit to suit my own convenience. I know it wasn't the optimum time for you, but you all rose nobly to the occasion and I do appreciate it. I've pick up lots of ideas, which I hope to incorporate in our little show."

July 27, 1937—Waters to Macintosh

"I have just received a letter from Blomfield telling me of the offer of an honorary membership in the Association of Anaesthetists of Great Britain and Ireland. Needless to say, I have written a very joyous acceptance."

August 24, 1937—Macintosh to Waters

"You having stimulated my interest in Snow, I am half-way through his book and very intrigued. I will send you two quotations in a later letter."

September 27, 1937—Macintosh to Waters

"One of the best things you have done for me is to make me read John Snow's book. What amazing observations and what a number of things he recorded which one imagined were comparatively recent observations. You did not mention it to me, but I see that on page 42 he has anticipated Miller in stating that the thoracic breathing goes before the diaphragmatic. On page 42, Snow writes, 'if the inhalation is continued after the symptoms just described are produced, the breathing is rendered difficult, feeble or irregular and is sometimes performed only by the diaphragm while the intercostal muscles are paralyzed.' Taylor‡ is with us and everyone seems to like him. He spent one morning with me at the dental hospital and in the afternoon we went off together to see Magill at the Brompton, during which time he told me that you had commissioned him to get a photograph of John Snow's grave."

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* Emory A. Rovenstine, 1895–1960, one of Waters' first residents, was later appointed Director of Anesthesia, Bellevue Hospital, New York, in 1935. Macintosh apparently expected to find copies of *On Chloroform* without much difficulty.

† H. K. Lewis and Co. Ltd., 136 Gower Street, London, closed on October 6, 1989, after being in business for 145 years.

September 29, 1937—Macintosh to Magill§

"Waters stimulated my interest in John Snow, whose wonderful book on chloroform I am ashamed to say I had not read until this year. Yesterday I went down to visit his grave at the Brompton Cemetery. The marble tombstone was erected in 1858 by his professional brethren and friends (Snow died unmarried). It was restored in 1895 by Sir Benjamin Richardson|| and friends [Figure 3]. I take it that this Richardson is the same man who wrote the preface to his book. The stone is crumbling and the inscription will soon become illegible. I made inquiries and was told it would take between £7 and £8 to put it in first-class condition. Would you as President of the Section this year care to open a subscription for this small amount, or do you think it should be left to the Society of Anaesthetists to deal with this question? It seems a pity that the stone of the first and probably the outstanding anesthetist of all time should be allowed to crumble beyond recognition. If you are sympathetic, I would propose limiting subscriptions to 5/-d. as this will stimulate interest in the subscribers and perhaps direct their attention toward his book. I feel Waters would not like to be left out of the list if you start it."

September 29, 1937—Macintosh to Waters

"Yesterday I went down to the Brompton Cemetery to see John Snow's grave. I looked in at the superintendent's office and asked about it. And immediately the man turned to his colleague and said, 'Here's another one wants to see that grave.' The plump man who took me there volunteered the information that last year a big American gentleman with a small lady asked to see the grave and that he told him that Snow lived 100 years before his time. So of course that clinched my diagnosis as to who the pair were [Waters and his wife]. Taylor visited the grave last week and so they were somewhat surprised when I and my two companions came on the same mission. I enclose a copy of a letter which I have written to Magill with which I hope you agree, although I am not sure as to your views on doing tombstones up."

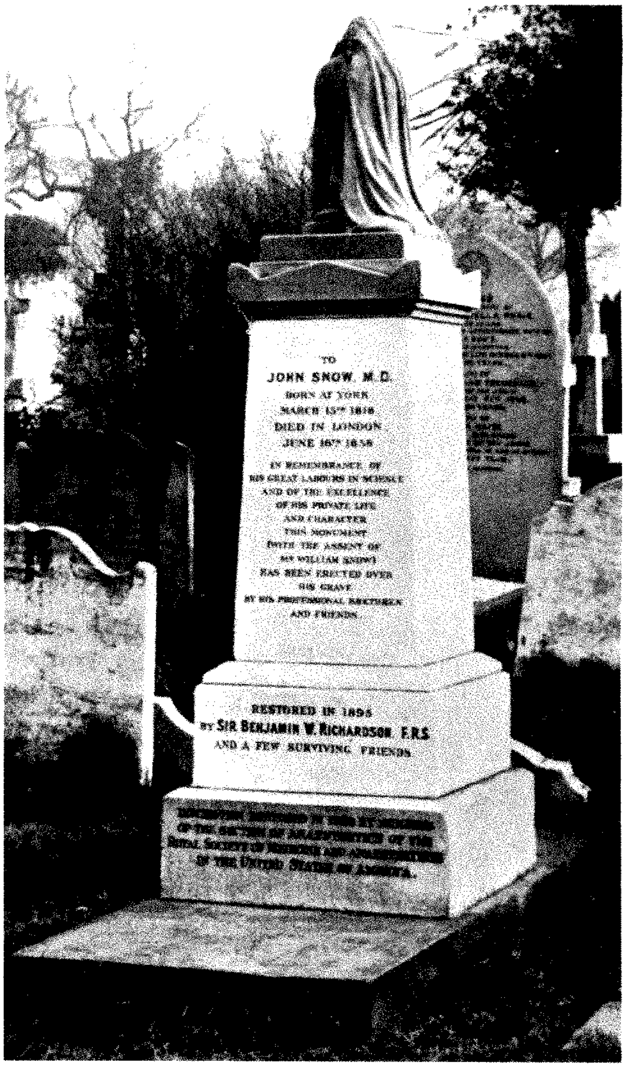
TO
JOHN SNOW, M.D.
BORN AT YORK
DIED IN LONDON
RESTORED IN 1895
BY SIR BENJAMIN W. RICHARDSON F.R.S
AND A FEW SURVIVING FRIENDS

Figure 3. Tombstone of John Snow in Brompton Cemetery, London. The inscribed year of his birth is incorrect: Snow was born in 1813, not 1818. The writing at the base of the tombstone reads: "Inscription restored in 1938 by members of the Section of Anaesthetics of the Royal Society of Medicine and [by] Anaesthetists in the United States of America." Reproduced with permission from Academic Press Inc. (London) Ltd. (Anaesthesia 1950;5:48).

September 30, 1937—Magill to Macintosh

"I have to thank you very much for drawing my attention to John Snow's grave. As President of the

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‡ Ivan Taylor, 1906–1966, one of Waters' residents at Madison, was working in Oxford in 1937.

§ Sir Ivan Magill, 1888–1985, was one of Britain's leading anesthetists from the end of the First World War until his retirement after the Second World War.

|| Sir Benjamin Ward Richardson, 1828–1896, anesthetist and friend of John Snow, wrote the introductory biography and edited *On Chloroform and Other Anaesthetics* after Snow's death.

Section [of Anaesthetics of the Royal Society of Medicine] this year, I should certainly feel it my duty to open a subscription as you suggest and you may be sure that I shall notify all concerned that the suggestion came from you. I shall have the matter placed on the agenda at the Council meeting of the Section on November 5. Incidentally I should be honored if you will dine with Nosworthy and myself on the evening of November 5 before the meeting (exact time and place later)."

October 4, 1937—Macintosh to Waters

"How curious that our letters dealing with the inscription over John Snow's grave should have crossed. I feel that I know you well enough to enclose three letters which I know will interest you. The first is from Magill which shows his reaction to the suggestion that the stone should be done up. The third letter I know will please you. It is from Dr. J. Blomfield, who is consulting anaesthetist to St. George's Hospital. In case you write to him, you did meet him when you were over last year and he attended your demonstration at University College Hospital. King (the apparatus manufacturer) found out that Blomfield had a copy of Snow's book and despite the fact that we are eager to get a copy for ourselves, we decided the first copy available must go to you. It is interesting that the book comes from St. George's where Snow's anaesthetics first attracted attention. We thought you would prefer the copy as it is instead of our putting a new cover on it. I think the best thing to do is to send it over with Taylor. One request: if you predecease me and I still have no copy, will you please think of me? Our opinion over here of your work can be judged by the fact that whereas Blomfield was willing to sell the book to Oxford, he was equally willing to part with the book without cost if it went to you."

October 19, 1937—Macintosh to Waters

"As you will see, we have had Snow's book covered after all. King and I felt that you would not like the book in your library doing nothing and that it will probably be read by all your assistants and therefore it was much better to have it bound here so that it could make a respectable present instead of it arriving in the ragged condition in which we found it.

"You will be pleased to hear that I have been promised a copy. I have made the acquaintance by letter of a Mrs. J. D. Richardson, who is the daughter-in-law of the old Sir Benjamin Richardson who wrote the preface to Snow's book and was instrumental in putting a tombstone up for him. I am writing to her shortly telling her of your great interest in Snow as I feel sure that she would like to get in touch with you."

October 21, 1937—Waters to Macintosh

"I was very happy to know that you have taken our friend John Snow seriously and that you are going to get his gravestone rehabilitated. I think it will be very fine if the Section on Anaesthetics can be responsible for it. I appreciate you letting me know about it. I can hardly say how much I appreciate the plans which you and Dr. Blomfield seem to be formulating in my behalf."

October 25, 1937—Macintosh to Waters

"I thought you would like to have a note letting you know that I have received my copy of John Snow's book. In a previous letter I know that I told you that I had got into touch with a Mrs. Richardson, who is the daughter-in-law of Sir Benjamin Richardson who wrote the preface of the book. I went up to see her the other evening. She is about sixty years old, a widow and very full of life. She has divided her house into two and in the upper portion lives a Mrs. Martin, also a widow aged about sixty, who is the only surviving child of Richardson. Mrs. Martin had kept most of Sir Benjamin's books, amounting to hundreds, and after looking through these for some time they came across my copy. They wanted to present me with the copy, but I must do something else about it because I feel they have fallen on hard times. Most of the books in the library were rather badly worn and in some cases the covers were almost torn off. I gather that this was because they had been used so often. Snow's book was in almost perfect condition, and this I should imagine was because Richardson, having edited it, probably never looked through it again."

October 29, 1937—Macintosh to Waters

"I am glad to hear from Taylor that Snow's book has arrived all right. You were kind enough to say that you would earmark it for me if in the meantime I could not lay my hands on another copy. As I told you in a previous letter, I have managed to do this, so naturally you will dispose of your copy as you see fit."

November 15, 1937—Waters to Macintosh

"Ivan [Taylor] and John Snow reached Madison safely, and I'm not sure which I was the most pleased to see. John was exhibited to the visitors the last of October. Some of them, I think, appreciated him, but none as much as I did. Can you find out how many copies were published originally and whether there were two editions? I have a feeling that the Surgeon General's Library copy here is different, in some respects, from the one in Edinburgh."

February 23, 1938—Macintosh to Waters

"I regret I have not yet found out any information as to whether two separate editions of John Snow's books were made. My secretary wrote to the original publishers of the book a short while ago, but had the letter returned. She is now making further enquiries from another firm of publishers and as soon as I have any information on the subject I will let you know. You will be interested to hear that although we have all been scouring the country for further copies of this book, none had come to hand until King informed me last week that he had just had word from a small bookseller in Paris telling him that he had a copy of the book for which he was advertising, and that it would cost him half a dollar!"

The following day the publisher, J. A. Churchill Ltd., wrote to Macintosh:

"The volume entitled 'On Chloroform and Other Anaesthetics, Their Action and Administration' by John Snow was published by us in the year 1858. Our records show that it was edited by a Dr. Richardson. The published price was 10s. 6d. and apparently about 450 copies were printed and sold. No second or subsequent edition was, so far as we are aware, issued."

Discussion

The correspondence between Waters and Macintosh between 1936 and 1938 reveals the close links that developed between leaders of our profession in the United States and Great Britain, partly as a result of their enthusiastic interest in John Snow. Their letters in the Waters correspondence files resolve the apparent inconsistencies of the inscription in Waters' 1858 edition of *On Chloroform and Other Anaesthetics*, which is now owned by the Wood Library-Museum. The handwriting of the message, and the order of priority of the signatures, is explained by the fact that although Macintosh started the search and King located the book, its presentation to Waters was made possible through the generosity of its owner Dr. Joseph Blomfield.

The authors thank the University of Wisconsin-Madison for access to archival material; Academic Press Inc. (London) Ltd. for permission to reprint Figure 3 from Anaesthesia 1950;5:48; Mr. Patrick Sim, Librarian at the Wood Library-Museum of Anesthesiology, for his interest and encouragement; Ms. J. Beinart of the Wellcome Unit for the History of Medicine, Oxford, for information from Sir Robert Macintosh's travel diaries; and Dr. R. H. Ellis and Dr. D. J. Wilkinson of St. Bartholomew's Hospital, London, England, for suggesting sources of reference.

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Clinical Reports

Anesthetic Management of a Patient With Systemic Carnitine Deficiency

Richard W. Rowe, MD, and Eric Helander, MD

Key Words: COMPLICATIONS, CARNITINE DEFICIENCY.

Carnitine deficiency, a rare condition associated with lipid storage disorders, was first described in 1973. Carnitine is an essential cofactor of long-chain fatty acid transport into the mitochondria. Carnitine deficiency appears in a systemic form and a myopathic form.

Systemic carnitine deficiency is characterized by a constellation of symptoms including recurrent encephalopathy, vomiting, and diarrhea. These attacks are associated with lactic acidosis, hypoglycemia, hyperammonemia, elevated blood levels of liver enzymes, coagulopathy, and low plasma levels of carnitine (1,2). Electron microscopy shows lipid vacuoles in type I skeletal muscle cells. Low plasma levels of carnitine in systemic form have been ascribed to a defect in hepatic biosynthesis of carnitine or to an excess of renal excretion.

Myopathic carnitine deficiency is characterized clinically by muscle weakness. Laboratory analysis shows decreased levels of carnitine in skeletal and cardiac muscle tissue and normal levels in the plasma. Electron microscopy shows the same pattern of lipid vacuoles in type I muscle cells. The derangement is thought to be due to reduced carnitine transport into muscle cells (3).

Case Report

The patient was a 5-yr-old girl who needed general anesthesia for dental rehabilitation. She had been a full-term infant born by cesarean section for breech position. Apgar scores were 9/10 but on day 3 she became dehydrated and acidotic, and evaluation for an inborn error of metabolism was begun. By the age of 2 yr, she had had multiple hospitalizations for vomiting, dehydration, and lethargy. Her admissions were typified by a clinical picture similar to that of Reye's syndrome: encephalopathy with severe hypoglycemia, lactic acidosis, hyperammonemia, increased blood levels of hepatic enzymes, hypoprothrombinemia, and mildly elevated muscle creatinine phosphokinase. On one occasion, she was comatose on admission with a serum glucose level of 6 mg/dL, markedly prolonged prothrombin time and partial thromboplastin time, and a blood pH of less than 7.15. She was given an intravenous infusion of 50% glucose, which increased her level of consciousness. She required fresh frozen plasma to correct her hypoprothrombinemia and sodium bicarbonate for her metabolic acidosis.

At age 2 yr, the patient was finally diagnosed as having systemic carnitine deficiency. A muscle biopsy showed lipid vacuolization of type I muscle fibers; electromyograms and electroencephalograms were normal.

Since that time, the patient has been taking 0.5 g of oral carnitine daily with normalization of her serum carnitine level (normal = 27–70 nmol/mL). Her diet was modified to include a higher percentage of carbohydrates and frequent snacks to avoid the threat of hypoglycemia. Her clinical picture has improved. Her only symptom at the time of the present admission was that she had been slightly lethargic in the morning before breakfast. She had no recent history of

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congestive heart failure, pseudohypertrophy or muscle wasting, dyspnea, petechiae, or bleeding. Growth and developmental milestones were essentially normal. She had a family history remarkable for a maternal aunt in Mexico who died of convulsions at age 3 yr but had no family history of anesthetic problems. She had no known allergies.

Physical examination showed an active and engaging child. Her chest was clear, she had no heart murmurs, the heart was of normal size, and she had a regular sinus rhythm. Her hemoglobin level was 10.3 mg/dL, and her blood carnitine level was 120 nmol/mL. Instructions had been given for her to have sugar-containing liquids 4 h before admission and to have her daily dose of carnitine.

On the patient's arrival at the hospital, an infusion of 5% dextrose in one-third normal saline solution was initiated. The patient was brought to the operating room where standard monitors were applied. After preoxygenation, anesthesia was induced with thiopental followed by atracurium. A nasotracheal tube was inserted, and anesthesia was maintained with oxygen, nitrous oxide, isoflurane, and fentanyl. Serum glucose levels were monitored throughout the procedure and kept between 120 and 180 mg/dL. The patient's vital signs remained stable: blood pressure = 90/50 mm Hg, heart rate = 100 beats/min, temperature = 36.3°–36.8°C, oxygen saturation > 99%, and $ETco_2$ = 27–41 mm Hg. The patient tolerated the procedure well and was extubated in the operating room. She was given droperidol postoperatively to prevent vomiting. She was able to take fluids orally, and her blood glucose level was stable at >100 mg/dL. After being observed for 8 h, the patient was discharged home that evening and had an uneventful recovery.

Discussion

Carnitine (β-hydroxy-γ-trimethyl-aminobutyric acid) is the essential cofactor in the enzymatic transport of long-chain fatty acids into the mitochondria in which they are oxidized. Synthesis of carnitine occurs in the liver and kidney but not in the cardiac or skeletal muscles. It is actively transported from the serum against a concentration gradient into muscle cells. Carnitine is combined enzymatically with fatty acyl coenzyme A by carnitine palmityl transferase I to form fatty acyl carnitine esters. This moiety is transported across the inner mitochondrial membrane through the enzyme system carnitine acylcarnitine translocase. Carnitine palmityl transferase II then regenerates carnitine and the fatty acyl ester for oxidation within the mitochondrial matrix.

The systemic form of carnitine deficiency can result in severe hypoglycemia as seen in our patient. Carnitine levels are low in the plasma as well as in the liver, muscle, and other tissues. As a consequence, peripheral tissues cannot use fatty acids for energy production, and the liver cannot adequately make ketone bodies as an alternative substrate for metabolism. Thus, tissues become glucose-dependent and their metabolism exceeds the liver's capacity for glucose production. During this metabolic crisis, there is evidence of severe liver failure with elevated blood levels of hepatic enzymes, lactic acidosis, hyperammonemia, hypoprothrombinemia, and hepatic encephalopathy. Severe cardiomyopathy has been reported in some patients with systemic carnitine deficiency. Therapy involves dietary supplementation with L-carnitine and a high carbohydrate diet.

Preoperative assessment of a patient with systemic carnitine deficiency should include evaluation of the neurologic status as well as the cardiopulmonary systems. If the patient is lethargic, the serum glucose should be immediately measured. Appropriate cardiac evaluation should be undertaken to determine if there is any cardiomyopathy.

Serum carnitine levels should be optimized preoperatively. Although carnitine levels remain adequate for 48 h after the last oral dose of carnitine, we recommend that patients receive their usual daily dose of carnitine on the morning of operation. It is advisable to start an intravenous infusion of glucose preoperatively and continue it intraoperatively with frequent measurements of serum glucose levels to assess adequate metabolic substrate availability and therefore avoid potentially catastrophic hypoglycemic episodes.

This patient underwent an uneventful general anesthesia. We used a nondepolarizing muscle relaxant without difficulty. It may be advisable to avoid the use of succinylcholine in these patients because of the unknown nature of the interaction of succinylcholine and of the patient's myopathy.

If these patients are referred for emergency operation while in a metabolic crisis, they must be adequately rehydrated with an appropriate amount of glucose. Blood levels of glucose and electrolytes as well as acid-base status must be evaluated, and corrected if necessary. Carnitine should be administered intravenously if the patient's neurologic function does not improve with glucose. Hypoprothrombinemia should be corrected with fresh frozen plasma.

The myopathic carnitine deficiency is characterized clinically by weakness, pathophysiologically by lipid storage myopathy, and biochemically by a low concentration of muscle carnitine despite normal serum and liver carnitine levels. A defect in carnitine transfer into muscle cells is thought to be the probable cause. This deficiency manifests itself in childhood with generalized proximal muscle weakness and can progress to respiratory failure. Cardiomyopathy leading to congestive heart failure and death have been reported. Corticosteroid therapy and L-carnitine administration is beneficial for some patients. Diets high in medium-chain triglycerides and low in long-chain fatty acids have been helpful, as medium-chain fatty acids are transported into the mitochondria independent of carnitine.

We know of no previously reported anesthesia experience with the systemic form of carnitine deficiency.

A previous anesthetic report has described the case of an 8-mo-old patient who had a myopathic form of carnitine deficiency and who underwent general anesthesia for tracheostomy (4). The anesthetic consisted of oxygen, nitrous oxide, and halothane, with spontaneous ventilation, and was well tolerated by the patient. Intravenous dextrose was administered intraoperatively.

Carnitine deficiency should not be confused with carnitine palmityl transferase deficiency, which has a clinical picture of myoglobinuria and exercise-induced myopathy. There have been reports of severe rhabdomyolysis occurring under general anesthesia with the latter disorder (5,6).

In summary, we have reported a case of anesthesia for a patient with systemic carnitine deficiency. Patients with this condition may have episodes of profound hypoglycemia and hemodynamic instability. However, with careful perioperative management of their blood glucose levels and acid-base balance, their anesthetic course should be normal.

We are grateful to Dr. Julian Irias and Meredith Bradley for their assistance.

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Psoas Block for Surgical Repair of Hip Fracture: A Case Report and Description of a Catheter Technique

Bruce Ben-David, MD, Ed Lee, MB, FFARSCI, and Milian Croitoru, MD

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—psoas block.

The earliest descriptions of a posterior approach to the lumbar plexus (1,2) used single-injection techniques. Like Chayen et al. (2), we have found the block particularly useful for operation of the hip (nailing, prosthesis, total hip replacement). However, the desire to provide postoperative analgesia prompted us to develop a continuous catheter version of the block. We report here a modification of the single-injection technique described by Parkinson and colleagues (3). In our modification, a catheter is placed into the psoas compartment to allow repeated "top-up" injections.

Case Report

A 79-yr-old, 80-kg woman with no clinically significant medical history was admitted for subcutaneous plating of an intertrochanteric femur fracture. On arrival in the operating room, monitoring with automatic blood pressure measurement, pulse oximetry, and electrocardiogram was instituted. The patient was positioned laterally with the operative hip up and was sedated with incremental doses of midazolam (a total of 2.5 mg) and fentanyl (a total of 150 μg).

The patient's back was cleansed with betadine, and the needle insertion site was identified by the intersection of a line drawn through the posterior superior iliac spine and parallel to the spine and a second line perpendicular to the first and through the spinous process of L-3. The insertion point was anesthetized with several milliliters of 1% lidocaine. A 16-gauge Secalon central venous pressure catheter (Viggo, Sweden) was prepared by inserting the metal needle of a 20-gauge Venflon intravenous (IV) (Viggo) catheter into the proximal end of the larger metal needle in the Secalon's hub (Figure 1). The central venous pressure needle was advanced a short distance into the skin at the insertion site, and the negative electrode of the nerve stimulator was attached to the exposed needle shaft protruding from the Secalon's hub. The positive end of the nerve stimulator was attached to an electrocardiographic electrode on the ipsilateral buttock, and the stimulator was set to pulse at 1 Hz. With the catheter directed parallel to the sagittal plane and slightly caudad, it was advanced until a 1-Hz pulsing was felt in the hand guiding the needle (quadratus lumborum stimulation). As the needle was advanced further a pop sensation was felt, after which, only slightly deeper, the muscles of the quadriceps group began twitching synchronously with the stimulator. Injection of 3 mL of 1% lidocaine with 1:200,000 epinephrine brought about a prompt and profound reduction in quadriceps twitching. Increasing the output of the nerve stimulator caused a resumption of the twitching, but an additional 5-mL injection of lidocaine obliterated that. The catheter was advanced beyond the needle, and the remainder of the lidocaine (a total of 40 mL) was injected through the catheter. An extension tube was connected to the catheter and extended over the patient's shoulder. The entire assembly was then taped into place.

The patient was then turned to the supine position and lifted onto the orthopedic frame. She was given 100 mg of thiopental to facilitate passage of a nasal airway that was then attached to the anesthesia circuit and to an $ETco_2$ monitor. The patient was allowed to spontaneously breathe 60% nitrous oxide in oxygen for the duration of the operation.

The patient's baseline heart rate on arrival at the operating room was 85 beats/min. It increased transiently to 95 beats/min 15 min after completion of the block and then returned to 70–80 beats/min for the entire 2-h operation. Blood pressure was 165/90 mm Hg on arrival at the operating room, decreased to

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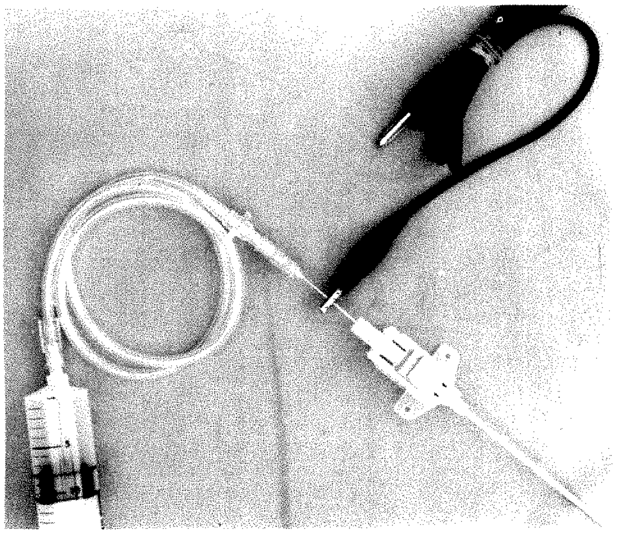

Figure 1. Assembly shows a 21-gauge needle inserted into the proximal end of the 16-gauge Secalon (Viggo, Sweden) central venous pressure catheter. Metal contact of the smaller needle inside the larger needle allows an electrical impulse to be conveyed to the Secalon needle tip. An alligator clip from the electrical stimulator is attached to the shaft of the 21-gauge needle. Intravenous extension tubing inserts into the hub of the 21-gauge needle.

140/75 mm Hg with sedation, and ranged between 120/60 and 145/70 mm Hg throughout the operation. She tolerated the procedure well with no evidence of discomfort or pain. One and a half hours after the initial injection, 30 mL of 0.33% bupivacaine with 1:200,000 epinephrine was injected. On discontinuation of nitrous oxide at the end of the operation, she awoke promptly and was alert and pain-free in the recovery room.

On the ward seven hours later, she began to complain of pain, and another injection through the catheter of 30 mL of 0.33% bupivacaine brought prompt relief. The patient sat up in a chair the following day and continued to have complete analgesia with no hemodynamic change. She did not require any narcotic during this period. The catheter was removed on the second postoperative day, and the patient had an uneventful recovery.

Discussion

There is an ongoing debate concerning the choice of regional versus general anesthesia for surgical repair of a fractured hip (4,5). The advantages of spinal (SA) and epidural anesthesia (EA) include a decreased incidence of deep vein thrombosis (DVT), a clearer postoperative mental status, and an avoidance of the early postoperative hypoxemia associated with general anesthesia (4,5). However, induction of SA or EA can be difficult in a hip fracture patient who may be unable to cooperate in properly flexing the lumbar spine because of pain. Spine calcification and degenerative spine disease may exacerbate the difficulty. A psoas block can be easily performed in the lateral position without a need for the patient to flex at the hip. Because the electrically induced twitching of the quadriceps muscles can provoke pain in the hip fracture patient, it is our practice to administer small doses of sedative and narcotic immediately before nerve localization and to have monitors, especially of Sa_{O_2}, already in place.

A disadvantage of SA or EA in many patients undergoing hip surgery is the risk of hypotension. These patients are frequently volume-depleted, and without close attention to fluid resuscitation and to loading these blocks can result in serious hemodynamic instability. Continuous spinal anesthesia (average highest level of block approximately T-8) has been associated, for example, with an average 30% decrease in mean arterial pressure (6). The majority of these patients required a vasopressor to support blood pressure. This occurred in spite of placement of a central venous catheter and of a urinary catheter preoperatively in all patients to optimize preoperative fluid status *plus* additional volume loading of 15 mL/kg intravenous crystalloid. In contrast, there is minimal hemodynamic alteration because the lumbar plexus block causes only a limited unilateral sympathectomy.

Although SA and EA reduce the incidence of DVT after hip operation, the not uncommon use of preoperative prophylactic anticoagulation (e.g., aspirin or subcutaneous heparin) is a dilemma for the anesthesiologist. The uncertain risk of causing a hematoma within the vertebral canal with consequent neurologic injury may dissuade the anesthesiologist from using SA or EA. The psoas block may be safer in this regard. Whether a lumbar plexus block would offer the same advantage with regard to DVT is unknown. The increased blood flow in the area of the unilateral sympathectomy and the effects of regional anesthesia on coagulation and fibrinolysis (secondary to an altered neuroendocrine response to operation) (4) suggest a likely benefit. In addition, the local anesthetics' inhibitory effects on platelet adhesion, aggregation, and release may have clinical usefulness as demonstrated by Cooke et al. (7) who showed that an intravenous lidocaine infusion during and after total hip replacement considerably reduced the incidence of DVT.

The majority of in-hospital deaths after hip fracture are due to pulmonary complications, embolism, cardiac disease, and sepsis (8). Early postoperative mobilization and "stir-up regimens" are known to decrease morbidity and mortality and facilitating these through profound analgesia is highly desirable. The use of a psoas catheter may provide such an alternative for postoperative analgesia. As illustrated by this case, the patient was out of bed soon after operation with no pain and no hemodynamic instability.

Two principal techniques have been described for posterior lumbar plexus blockade. In the psoas sheath block (PSB) technique, the needle is inserted 3–4 cm lateral to the spinous process of L-3, is passed caudad to the transverse process of L-3, and is advanced 1.5–2 cm beyond the transverse process (3). The needle is thus positioned within the psoas muscle and its sheath. Because the lumbar plexus is formed within the body of the psoas muscle, local anesthetic injected within the psoas sheath will produce blockade of the lumbar plexus.

An alternative approach is the psoas compartment block (PCB) described by Winnie and colleagues (1) in which the needle is positioned at the intersection of the intercristal line and a line drawn parallel to the spine through the posterior superior iliac spine. The needle is then advanced perpendicular to the coronal plane between the transverse processes of L-4 and L-5 deep to the fascia iliaca on the anterior surface of the quadratus lumborum. At the level of L4–5, the nerves to the lumbar plexus have already emerged from the psoas and lie in this fascial compartment between the psoas and quadratus. Injection of local anesthetic here in the potential space between the quadratus and the psoas accomplishes simultaneous block of nerves formed from the lumbar plexus (lateral cutaneous nerve, femoral nerve, genitofemoral nerve, obturator nerve, and the lumbosacral trunk).

When success rates were compared between these two techniques (PSB and PCB), they yielded similar results (PSB: 1/25 failure, PCB: 2/25 failure) (3). Dalens et al. (9) compared a modified PSB technique (the needle being placed more medial than in the original description of Chayen et al. [2]) with Winnie's PCB technique. In the former group, there was 1 failed block in 25 patients and there were no failures in the latter group. However, it is not enough to compare only the incidence of failed blocks because, as both reports demonstrated, there is a significant difference in the incidence of the block being complicated by epidural blockade.

Muravchick and Owens (10) reported a case of psoas block complicated by total epidural blockade. Within 10 min of injection, their patient was unresponsive and apneic and required tracheal intubation, artificial ventilation, and blood pressure support with ephedrine. The studies by Parkinson and by Dalens and their associates also show a marked incidence of this complication, unintentional epidural anesthesia, although in neither study did a patient have a sensory level above T-6. In the study by Parkinson et al. (3), epidural anesthesia developed in 4 of 25 patients with the PSB technique, whereas with the PCB technique, this was seen only once (and in that patient the epidural block extended only to T-10). In the study by Dalens et al. (9), epidural block developed in 22 of 25 patients with the modified PSB technique, whereas with the PCB technique, none of the patients had an epidural block. Dalens and coworkers concluded that the modified PSB technique is really a block comparable to and equivalent to epidural blockade. The apparent mechanism is spread of local anesthetic proximally into the paravertebral space rather than needle placement directly into the epidural space. This is supported by all patients having residual lumbar plexus blockade when the epidural wore off.

If a block is to be clinically useful, it must have a high success rate, be easy to perform, and have minimal complications. Therefore, it is important to consider the elements of posterior lumbar plexus block that make the block more likely to succeed as well as to consider the ways to minimize or avoid epidural blockade. In any event, the risk of epidural blockade mandates that only qualified personnel inject local anesthetic solution into the catheter (e.g., in the ward), that patients be closely monitored afterwards, and that one must be prepared to deal with the complication in whatever setting one is making an injection.

In avoiding an epidural block, the PCB technique may be superior although data are insufficient at this point to rule out the use of the PSB technique. What is clear is that there is a higher risk of epidural block with medial positioning of the needle (9). We believe that the use of peripheral nerve stimulation (PNS) for posterior lumbar plexus block not only provides for a distinct end point and a high success rate, but also provides clues to help avoid epidural block. Dalens et al. (9) found a strong correlation between lumbosacral trunk stimulation (flexion-extension movements of the ankle and toes) and epidural blockade. As the lumbosacral trunk (L-4 to L-5) is the most medial component of the lumbar plexus, it is the closest to the paravertebral space. Large volumes of local anesthetic injected medially would be more likely to spill over into the paravertebral space than anesthetic injected more laterally. It is recommended that isolated stimulation of the femoral nerve (quadriceps twitch only) be sought as this nerve is centrally located in the plexus.

Peripheral nerve stimulation may have a higher success rate when used with sheathed needles. An unsheathed needle may cause false localization owing to stimulation by the needle shaft. A sheathed needle allows more precise placement because the current exits only at the needle tip. Chayen et al. (2) used a loss-of-resistance technique to judge the proper depth of needle placement for local anesthetic injection and reported a 10% failure rate. Parkinson et al. (3) used PNS with unsheathed needles and reported three failures in 50 patients despite obtaining a quadriceps twitch. In fact, he noted that this problem may have been rectified by using sheathed needles. Dalens et al. (9) *used* sheathed needles and reported only one failure in 50 patients. It is not stated in these reports whether the authors used a test dose with PNS to verify proper needle positioning.

Our psoas catheter technique is an adaptation of a technique we regularly use for placement of peripheral nerve block catheters (e.g., continuous brachial plexus blocks). In this latter technique, the needle introducer from a plastic IV cannula is removed and inserted into the proximal end of an IV cannula four gauges larger (e.g., the needle from a 22-gauge IV cannula is inserted into the proximal end of an 18-gauge IV cannula), fitting snugly into the shaft of the metal needle of the larger IV cannula. This arrangement not only allows for cannula placement and an electrically sheathed needle for nerve localization but also provides the ability to maintain an uninterrupted and unaltered electrical stimulus while injecting a small "test dose" of local anesthetic to verify proper needle position. Our choice of this particular catheter was simply that it was the longest IV cannula (catheter over a needle assembly) available to us. Catheter placement can be achieved by using an epidural needle and catheter as has been done for continuous lumbar sympathetic blockade (11). This method, however, has the disadvantage of using an unsheathed needle. We are unaware of any sheathed epidural needle currently available on the market.

In summary, we report here a technique of continuous posterior lumbar plexus block applicable for both intraoperative anesthesia and postoperative analgesia. We have used this technique successfully with both the PSB and the PCB approaches. A thorough understanding of the anatomy, proper technique, use of peripheral nerve stimulation with test dose verification of proper needle placement, and use of sheathed needles all contribute to a high success rate. Consideration should be given to the potential complication of epidural block as it applies to monitoring, technique, and use of PNS. The excellent anesthesia and analgesia and the hemodynamic stability seen with this block make it a valuable addition to the armamentarium of the anesthesiologist.

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Contamination of a Hospital Oxygen Supply

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Key Words: OXYGEN, DELIVERY SYSTEMS—contamination.

There are a number of possible sites where difficulties might arise in hospital gas delivery systems (1). Sprague and Archer (2) list 14 different causes of hypoxic gas mixtures for anesthesia systems alone. Although problems with contamination of hospital central oxygen supplies have been known to occur, fortunately they are rare. In one reported instance, gross pollution of the oxygen supply with argon resulted in serious patient injury (3). We now describe an episode involving the central oxygen supply at a teaching hospital that illustrates another unreported manner by which contamination of oxygen supplies may occur. More important, this contamination was not detected by the usual oxygen monitoring systems.

Incident Report

The episode began in mid-morning as an oxygen supply truck delivered liquid oxygen to the main holding tank of a large teaching hospital. The truck served as the source of gaseous oxygen to the hospital while the liquid oxygen was being pumped into the main holding tank. During the next half-hour, two patients noticed a peculiar smell in the oxygen being administered to them and reported this to the nursing staff. At about the same time, an employee of the Biomedical Engineering Department smelled a malodorous gas issuing from the wall oxygen supply while calibrating an instrument. He reported this to his supervisor who immediately notified Cardio-Respiratory Services of potential contamination of the hospital oxygen supply. The odor suggested that the contaminant might be carbon tetrachloride. The directors of Cardio-Respiratory Services elected to transfer all patients receiving oxygen from the wall system to tank supplies, starting in the operating room and intensive care units and then progressing to other patient care areas. Surgical procedures in progress were continued using tank oxygen, but all elective operations requiring anesthesia were postponed pending resolution of the problem. The Emergency Department was notified to ensure that any incoming patients who needed oxygen would receive it from tanks rather than from wall oxygen outlets. Within 25 min of notification of the Biomedical Engineering supervisor, all patients were reported to be receiving tank oxygen. A crisis management group consisting of representatives from the University Environmental Health and Hospital Engineering Departments, Cardio-Respiratory Services, Nursing Services, and Materials Services was formed to coordinate the response to the crisis.

Because the origin of the problem was not yet identified, there was no hint as to its potential duration. The Materials Services Department began seeking additional supplies of tank oxygen from various sources within the metropolitan area. Within 3 h, sufficient tanks were obtained to ensure oxygen supplies for the next 24 h.

The oxygen supply company was contacted and after some delay suggested that the contaminant might be a solvent commonly used by their employees to clean delivery apparatus. The University Department of Environmental Health and Safety had begun chemical analysis of the contaminated wall oxygen as soon as it was notified of the problem. Two hours after the truck started delivering oxygen, the contaminating substance was confirmed to be the organic compound 1,1,1-trichloroethane (CCl_3CH_3).

At roughly the same time, nursing members of the crisis management team began a walk-through of all patient care areas in the hospital to ensure that wall oxygen was no longer being administered to patients. Despite previous efforts, two patients still were receiving wall outlet oxygen, and they were changed to tank gas. Gradually, patients in the intensive care

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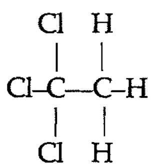
units whose respirations had been manually controlled with 100% oxygen since the outset of the exigency were switched to Servo ventilators driven by compressed air, oxygen from tanks being added to the inspiratory limb to achieve the prescribed inspired oxygen concentration.

Approximately 3 h into the crisis, it was determined that the highest concentration of trichloroethane in the wall system at that time was 400 ppm. This was assumed to be well below the peak levels achieved during the initial contamination. The source of the contamination was the residual cleaning fluid in the hose that had connected the delivery truck to the hospital to maintain the oxygen supply during delivery of liquid oxygen to the main hospital storage tank. The truck driver had confirmed that he might have forgotten to flush the apparatus. Fortunately, only the high pressure gas system in the main hospital building had been contaminated. The liquid oxygen storage tank that was being replenished during the pollution of the hospital system was clean, and oxygen supplies in other hospital buildings had not been affected. These uncontaminated areas were allowed to resume their normal activities at this time. The crisis management group decided to depressurize and flush the high pressure oxygen system in the main hospital building to eliminate the trichloroethane. Once purity had been established by chemical analysis, the system would be repressurized. This system flush was begun in the early afternoon. It was estimated that to eliminate all traces of trichloroethane, each individual wall outlet should be flushed for at least 30 s. This tedious process continued over the next 10 h. After ensuring that no trichloroethane could be measured in the system, the Hospital Engineering Department notified all patient care areas including the operating rooms that oxygen was once again available from wall outlets, i.e., about 15 h after the contamination was first reported.

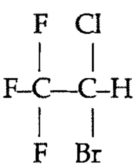
Discussion

Trichloroethane (a commonly used cleaning solvent) is a fairly benign halogenated hydrocarbon with a chemical structure roughly similar to halothane:



$\mathrm{Cl{-}CCl_2{-}CH_2{-}H}$

trichloroethane



$\mathrm{F{-}CF_2{-}CClBr{-}H}$

halothane

In fact, in much higher concentrations than those achieved during this episode, trichloroethane has mild anesthetic properties. Toxic effects, again in much higher doses than were seen during this incident, include conjunctival irritation, central nervous system irritability, hallucinations, changes in motor activity and psychophysiologic tasks, nausea, vomiting, and diarrhea (4). When CCl_3CH_3 is administered chronically in high doses, damage to liver and kidneys is observed in experimental animals (4). The drug may be absorbed by inhalation, by ingestion, or percutaneously. Data on potential carcinogenic properties are inconclusive. In high concentrations, CCl_3CH_3 has the potential to explode at temperatures above 25°C and also may emit toxic fumes under these circumstances.

The present incident differed from those previously reported in the literature in two important ways. First, no patients suffered any apparent ill effects. Second, even though wall oxygen concentration was being monitored continuously in the intensive care units, the amount of trichloroethane contaminating the oxygen did not lower the oxygen concentration enough to be detected by these relatively imprecise instruments.

Discussions with the oxygen supplier lead us to conclude that the driver of the supply truck involved had not followed established company procedure in that he neither flushed his hoses with nitrogen after cleaning them with trichloroethane at the supply facility nor with oxygen before delivery at the hospital. The fact that this incident occurred in the face of the oxygen delivery service's established safety and quality control procedures engenders concern about future patient safety. Oxygen delivery systems must be clean, but a nontoxic cleaning solvent is not available. Furthermore, with current technology it does not appear possible to devise a practical method of detecting low-dose contamination of a hospital's oxygen supply system with cleaning solvent or any other noxious substance. Accordingly, delivery procedures must be revised to achieve maximum safety.

One approach would be to revise the procedure so that a delivery vehicle could contaminate only one system during the delivery of liquid oxygen, i.e., during oxygen delivery the hospital supply should be maintained by a secondary source of confirmed purity rather than by the delivery vehicle. This secondary source should be capable of meeting hospital requirements for oxygen for a period of hours during which the contents of the main holding tank could be tested for contamination. Although it should prevent patient exposure to contaminated oxygen, this approach would not eliminate the possibility of pollution of the main hospital liquid oxygen source and the ensuing hectic search for additional pure oxygen supplies. Obviously, the ultimate goal is the detection of trace contaminants *before* polluting any of the hospital systems. As the incident described above demonstrates, it is not sufficient to sample the oxygen as it is loaded into the delivery vehicle; one must rule out contamination at the point of entry to the hospital systems.

Trace amounts of pungent organic compounds can frequently be detected by alert employees as was the case in the present episode and also in that reported by Eichhorn et al. (5). Chemical analysis of the contaminant may then be performed using infrared absorption analysis as in our case, or by gas chromatography after a complex condensation procedure as reported by Eichhorn et al. (5). Such instrumentation is not immediately available in all hospitals and, furthermore, exact identification of the offending substance may be prevented by overlapping absorption spectra. The difficulty associated with identifying inorganic compounds is even greater than with organic contaminants. Mass spectrometry (3) or x-ray microprobe analysis (5) have been used to identify contaminants. However, quadripole mass spectrographs are expensive and delicate instruments and not sufficiently reliable that one could count on their being on-line during every oxygen delivery. X-ray microprobe analysis is not a generally available technique and, furthermore, has several limitations (4).

In the situation presented, the probable identity of the compound was obtained from the oxygen supply company, and confirmation of identification and quantitative analysis was undertaken using a Wilks-Miran IA infrared gas analyzer. However, when one has no idea of the identity of the contaminant, it is difficult to envision a system that would be sensitive enough to detect minute quantities of the almost infinite array of potentially contaminating substances and yet rugged enough to be used at an oxygen storage site that is often, of necessity, at some distance from hospital buildings. Currently available instruments are so delicate that for all practical purposes they would need to be housed and used in the hospital itself.

Although it is unlikely that episodes similar to the one described here will occur with any frequency, the fact that contamination did occur in the face of procedures established to prevent such situations leads one to believe that the potential for another similar incident, possibly with more severe consequences, exists. Enormous amounts of time and effort were expended in the present instance after the contamination to ensure that the pollutant was completely removed and that patient safety had been assured. Expenditures for the hospital were primarily the result of the large number of employee hours required to flush every outlet in the main hospital building and the procurement of sufficient numbers of oxygen cylinders to ensure adequate supplies for at least 24 h. Given the current fiscal climate, repetition of such an episode needs to be avoided not only for patient safety but for financial considerations.

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Letters to the Editor

Statistical Analysis of Nitrous Oxide and Enflurane Interactions

Key Words: STATISTICS, DRUG INTERACTIONS. INTERACTIONS (DRUG), STATISTICAL ANALYSIS.

To the Editor:

In a recent article Cole et al. (1) conclude that the effects of enflurane and nitrous oxide (N_2O) in male Sprague–Dawley rats are nonadditive. By using linear extrapolation from the three lowest N_2O values they conclude that there may be a relative antagonism between these agents at higher N_2O concentrations. In an accompanying editorial Eger (2) disputes the conclusion that Cole's data supports nonadditivity. He uses two arguments: (a) that it is improper to choose arbitrarily the three lowest N_2O concentrations for the basis of statements about the entire range of N_2O values; and (b) by treating the data for 30% N_2O as "outliers," an excellent linear fit through the remaining data points results.

Three points deserve to be made:

(a) If all the data of Cole et al. are subjected to a standard lack-of-fit test (3,4) for linearity we will reject the hypothesis of additivity at the 0.1% level of significance.

(b) The interpretation of this nonlinearity (nonadditivity) is speculative without data for the full range of N_2O values (up to MAC 1), but is consistent with a synergistic interaction between N_2O and enflurane.

(c) In agreement with Eger, one should not extrapolate from data at one end of the range to data at its other end. In disagreement with him, rejecting inconvenient data points as outliers may obscure the true nature of the relationship between the variables under study.

The lack-of-fit test (LOFT) is a standard statistical procedure that can be used to test the appropriateness of a linear regression model whenever there are repeated X values. Cole's data are divided among six groups with 14 data points per group. If the X (N_2O) values are treated as constant within each group, LOFT can be performed using the processed data in Table 2 of Cole et al. The regression equation derived using all $n = 84$ data points is $Y = -0.00929X + 2.259$. The residual sum of squares (SS) for this fitted line (see Figure 1) can be divided into two parts: a pure-error SS based on the variation in Y within each of the six groups, and a lack-of-fit SS based on the distance of the group means from the regression line. If the linear regression model $Y = \beta X + \alpha + \epsilon$ is correct, then both the lack-of-fit mean square (MS) and pure-error MS will be estimates of the variance of ϵ, and their ratio will have an F-distribution. The results of this test are summarized in Table 1 (see Appendix for details and calculations).

This result leads us to reject the hypothesis of additivity at the 0.1% level of significance. The nature of this nonadditivity is not at all clear from the regression line in Figure 1. There is certainly no apparent antagonism at the three higher N_2O values, and although the data point for 30% N_2O is further than any of the others from the regression line, it could be very misleading to declare this point an outlier in an attempt to produce a more linear appearance for the remaining points (5). One hypothetical iso-MAC-ogram that would be consistent with the data displays synergistic effects of varying degree over the entire range of

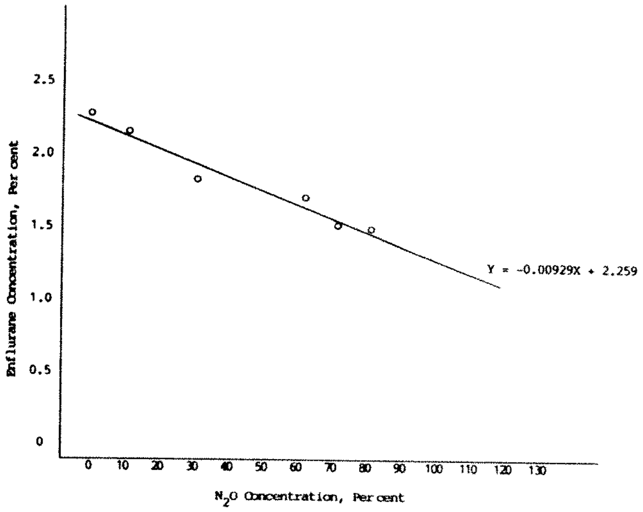

Figure 1. Determinations of enflurane MAC in the presence of various concentrations of N_2O using the data in Table 2 from Cole et al. The *open circles* represent the bivariate means for the six groups. The *solid line* represents the linear regression equation for these data.

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Table 1. Analysis of Variance (Showing Lack-of-Fit)

Source	df	SS	MS	F ratio
Regression	1	6.757		
Residual	82	1.579		
Lack of fit	4	0.340	0.085	F = 5.35
Pure error	78	1.239	0.016	($P < 0.001$)
Total (corrected)	83	8.336		

SS, sum of squares; MS, mean square.

the variables, and is shown in Figure 2. Because of the shape of the curve, any regression line fitted to low values of N_2O will automatically "sink below" data for higher N_2O values, and linear fits through a few low and a few high N_2O points will "rise above" data for intermediate N_2O values. Thus the data can be explained without incurring antagonism at high N_2O values or outlier effects at intermediate values. To confirm the existence and/or nature of this synergy, *data*—not extrapolation—for N_2O values up to MAC 1 are needed because it is certainly possible to design other curves to fit the data for N_2O values of 80% or less.

Appendix

If we have I groups each with J data points, so that there is a total of N = IJ data points (X_{ij}, Y_{ij}) for i = 1, 2, . . . , I and j = 1, 2, . . . , J, and if we suppose that X_{ij} is constant within each group so that $X_{ij} = X_i$, then SS_{PE}, pure error SS, can be computed as

$$SS_{PE} = \sum_{i=1}^{I}\left(\sum_{j=1}^{J} Y_{ij}^2 - \frac{1}{J}\left(\sum_{j=1}^{J} Y_{ij}\right)^2\right) = \sum_{i=1}^{I} (J-1)S^{i}_{y/x_2}$$

$$= 13\,(0.17^2 + \ldots + 0.12^2) = 1.239.$$

SS_T, total (corrected) SS, can be computed as

$$SS_T = \sum_{ij} Y_{ij}^2 - \frac{1}{N}\left(\sum_{ij} Y_{ij}\right)^2 = \sum_{ij} Y_{ij}^2 - \frac{1}{N}\left(J\sum_{i=1}^{I} \bar{Y}_i\right)^2,$$

where

$$\bar{Y}_i = \frac{1}{J}\sum_{j=1}^{J} Y_{ij}$$

$$= SS_{PE} + J\sum_{i=1}^{I} \bar{Y}_i^2 - \frac{J^2}{N}\left(\sum_{i=1}^{I} \bar{Y}_i\right)^2$$

$$= SS_{PE} + J\left\{\sum \bar{Y}_i^2 - \frac{1}{I}\left(\sum \bar{Y}_i\right)^2\right\}$$

$$= 1.239 + 14\left\{21.3763 - \frac{1}{6}(11.19)^2\right\} = 8.3362.$$

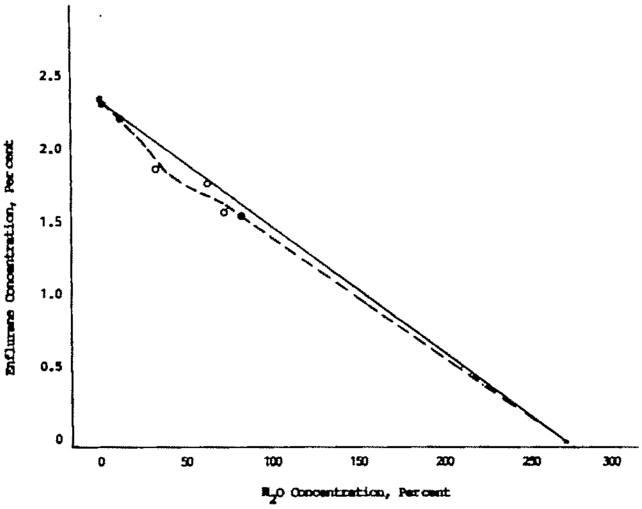

Figure 2. The *open circles* represent the group means from Table 2 of Cole et al. The *dashed line* represents a hypothetical iso-MAC-ogram consistent with these data. The *solid line* represents a hypothetical iso-MAC-ogram if the effects of N_2O and enflurane are additive at MAC 1.

The other sums-of-squares are calculated in a similar fashion.

Although the X values within each group are not actually constant, only a very small error in the calculations is produced by treating them as such because the variation in X within each group is extremely small compared with the difference in X scores between groups. If, however, the raw data are available, an accurate SS_{PE} can be derived for each of the six groups by using group-specific linear regression lines, and setting the residual SS for each group about its line equal to that group's contribution to SS_{PE}. There will be a loss of one degree of freedom per group for SS_{PE} if this is done.

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In Response:

Using the LOFT, Hochman affirms our observation that N_2O and enflurane are not linearly additive in rats (1). His proposed use of the LOFT is a meaningful improvement over the statistical methods we employed in that an assumption regarding antagonism/synergism is not implied. Although our second figure implies an assumption of antagonism at higher N_2O concentrations, in our discussion we specifically addressed the difficulty of interpreting these data as evidence for either antagonism or synergism.

We agree with Hochman's contention that extrapolation from a few data points is inappropriate. However, it should be noted that our observation of nonlinear additivity is derived from 42 independent observations (14 animals at each of the three lower N_2O concentrations). Furthermore, we concur that a complete understanding of the anesthetic interaction between inhaled agents will require hyperbaric studies to determine the entire N_2O dose-response curve. Nonetheless, Hochman's arguments, in combination with our original report (1), provide evidence that is inconsistent with the prevailing assumption that N_2O combines linearly with inhalational agents to produce anesthesia. In addition, we have recently reported new data that exhibit a similar pattern of nonlinear summation for combinations of N_2O and enflurane, halothane, or isoflurane (2). An understanding of the mechanisms behind these observations will require additional studies.

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Concentration of Halothane in Krebs' Medium

Key Words: ANESTHETICS, VOLATILE—halothane.

To the Editor:

We recently published our results of normal human muscle contractures induced by halothane or caffeine (1). We now present results of the halothane concentration achieved in the Krebs' medium in that study.

After equilibration with halothane (5 min bubbling), 1 mL of Krebs' solution was injected into 2 mL of hexane and analyzed in a gas chromatograph with an autoinjector, cross-linked 10 m × 0.53 mm × 2.0 μm capillary column, nickel 63 electron capture detector, with carrier gas–argon/methane (95%/5%), oven temperature of 150°C, injector temperature of 200°C, detector temperature of 300°C, and gas flow rate of 42 mL/min. Two microliters of the hexane solution was injected into the gas chromatograph for analysis. The calculation for percent halothane uses the following equation (PPM is multiplied by 2 because of the 1 to 2 dilution):

$$\% = \frac{\text{PPM} \times 1.86 \times 10^{-3} \times 22.4 \times 760 \times 310}{197.39 \times \lambda \times 713 \times 273},$$

where PPM is the parts per million value from the gas chromatograph, 1.86 is the specific gravity of halothane, 10^{-3} is a factor converting millimoles to moles, 22.4 is the molar gas volume, 197.39 is the molecular weight of halothane, and the remainder are pressure/temperature correction factors from STPD to ATPS. The λ for Krebs' solution approximates 0.7. One percent halothane vapor yielded 0.90% ± 0.03% (mean ± SE) in Krebs' solution; 2% halothane vapor yielded 1.58% ± 0.03% in Krebs' solution; and 3% halothane vapor yielded 2.58% ± 0.05% in Krebs' solution.

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Epidural Infusions: A System to Reduce Unintended Injections

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—postoperative pain. PAIN, POSTOPERATIVE—epidural analgesic.

To the Editor:

Anesthesiologists, with increasing frequency, are treating postoperative pain using epidural infusions of local anesthetics and opioids. In our practice, the anesthesiologist often uses epidural medications as a component of the intraoperative anesthetic management. Postoperatively a continuous infusion of either morphine-bupivacaine or fentanyl-bupivacaine provides analgesia.

Usually we locate the epidural catheter connector on the anterior chest wall. Because of its position, we fear that the

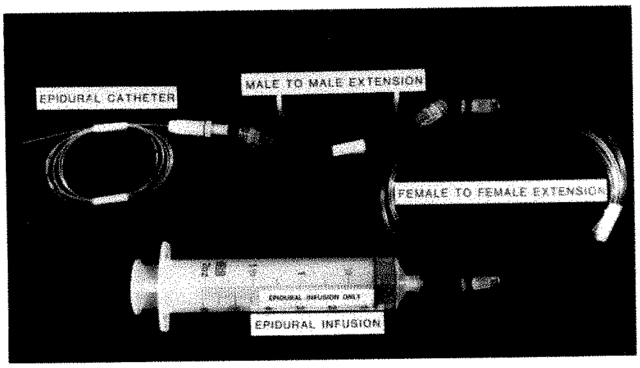

Figure 1. The male-to-male extension is compatible only with the female-to-female tubing.

catheter connector will be mistaken for one leading to a central intravenous catheter or that the venous connector will be mistaken for the epidural connector because both may be placed in the same area of the body. To avoid infusing a solution intended for venous administration into the epidural catheter or infusing an epidural infusion into a venous catheter, we have devised a system that reduces the likelihood of this error.

The anesthesiologist caring for the patient who will have an epidural infusion postoperatively for pain management orders the anesthetic-opioid solution either preoperatively or after induction of anesthesia. The pharmacy delivers the solution to the postanesthesia care unit before the patient's arrival. The patient's nurse attaches a 30-cm male-to-male tube (NAMIC, Angiographic Systems Division, Glen Falls, N.Y., model 90702122) that has been flushed with the epidural infusate to the epidural catheter connector. This catheter and tubing connection is then taped to the patient's chest. The epidural infusion connects to the extension tube via a 90-cm female-to-female connecting tube (NAMIC, Angiographic Systems Division, model 62030321) (Figure 1). No infusion ports exist along the infusion tubing. The nurse also attaches two fluorescent bright pink labels stating "EPIDURAL INFUSION ONLY" to each of the connecting tubes (Shamrock Scientific Specialty Systems, Bellwood, Ill.).

When the solution is changed, the nurse changes the tubing up to the male-to-male connector. With this connecting tube in place, only female-to-female tubing designated solely for epidural infusions can be used to attach infusates. As a result, intravenous solution infusion sets that routinely terminate with a male connector cannot easily be connected to the epidural catheter. The absence of infusion ports makes the system appear markedly different than the intravenous infusion system used in the hospital and prevents the accidental administration of "piggyback" solutions into the system. The short connecting tube also alleviates the need to manipulate the standard, easily disconnected epidural connector. The male-to-male connecting tube is stored only in the postanesthesia care unit and is unavailable to the general hospital personnel. Only the female-to-female tubing is available to the regular nursing staff.

Before the institution of this connecting system, two epidural infusions in our hospital were mistakenly connected to a venous catheter. Since the institution of this system, this error has not reoccurred. The major disadvantage of this system is the need to untape the epidural connector if a bolus of narcotic or local anesthetic is needed to improve the analgesia or test the catheter. Stocking additional infusion tubing within the hospital may also create a problem. However, these disadvantages are easily overcome and are overshadowed by the need to make epidural analgesic infusions safe.

This system makes unintended administration of a solution into the epidural catheter difficult. The labels provide additional notice to the patient's caretakers of the presence of a epidural analgesic infusion. As with most equipment, creative but uninformed minds can overcome the most fail-safe system. Education, vigilant nursing care, and close physician supervision remain the crucial safety measures.

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Intravenous Ketamine in the Isolated Upper Extremity of Humans

Key Words: ANESTHETICS, INTRAVENOUS—ketamine.

To the Editor:

I have read with interest the paper by Durrani et al. on the use of ketamine for intravenous regional anesthesia (1).

The topical anesthetic effect of ketamine was established by Chen et al. in 1959 (2), McCarthy et al. in 1965 (3), and Dowdy et al. in 1973 (4). In a study published by us, in preliminary form, in Spanish (5) in 1978 and later published in full in 1979 in English (6), we reported the neuromuscular blocking properties of intravenous ketamine in the human isolated arm. The level of anesthesia was not investigated in this paper.

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A Cordless Infrared Headphone System for Monitoring Heart and Breath Sounds

Key Words: MONITORING, HEART AND BREATH SOUNDS—headphones.

To the Editor:

In recent years new methods of continuous monitoring of heart and breath sounds have become available to anesthesiologists (1–3). Unfortunately, until recently, most of these systems have been expensive ($200) and/or require continuous contact with the patient.

For approximately 2 yr and in more than 500 patients we have been using a cordless infrared headphone system (wire-free Cordless Audio Systems, Berkey Marketing Company, Greenwich, Conn., model W8937R) with great success. The system is composed of a wire-free infrared transmitter that converts sound to an infrared signal. A headphone receiver converts the infrared signal to clear and precise sound with minimal interference from electrocautery or other transmitters. The headphones require one 9-V battery. The transmitter runs off 110-V alternating current and the microphone may be adapted to a precordial chest piece or esophageal stethoscope quite easily.

We have also tested similarly priced FM wireless headphone systems and have found the quality of sound to be inferior to the infrared model used at our institution. In addition, unlike the FM wireless monitors, this product will not transmit sounds from surrounding operating rooms. The infrared transmitter is also sensitive enough to detect early changes in both heart and breath sounds while enabling the anesthesiologist to attend to the patient's needs without being tethered to the patient.

As in any system, there are limitations to this infrared signaling device. Heart and breath sounds are somewhat diminished if the anesthesiologist is situated behind the transmitter unit. This is easily avoided by clipping the transmitter to the anesthesia machine. In addition, electrocautery interferes with the fidelity of sound transmission, although much less than with the FM type.

In conclusion, we have found the cordless infrared headphone system to be a safe, practical, and cost-effective means of monitoring heart and breath sounds in the anesthetized patient. The transmitter may be purchased for approximately $80 through many electronics catalogs.

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Pulse Oximetry in Confirmation of Correct Tracheal Tube Placement

Key Words: INTUBATION, TRACHEAL. MEASUREMENT TECHNIQUES, PULSE OXIMETRY.

To the Editor:

Capnography has been advocated as the best method to confirm placement of a tracheal tube (1). Pulse oximetry has been said to provide only a late indication of incorrect tracheal tube placement because preoxygenation may prevent hypoxia for several minutes (2). The following case report illustrates the utility of pulse oximetry in verifying correct placement of the tracheal tube at a time when our capnograph failed.

Case report. The patient was a 76-yr-old woman who had undergone resection of a recurrent thyroid mass on several occasions. She was thought to have bilateral recurrent laryngeal nerve injury, and she required a tracheal tube for respiratory support. She was brought to the operating room for an attempted tracheal extubation. Three milligrams of diazepam were administered intravenously, and 10% lidocaine was applied topically to the oral cavity. Monitors included electrocardiogram, a pulse oximeter, a precordial stethoscope, a capnograph, and a noninvasive automated blood pressure apparatus. While spontaneously breathing 100% oxygen, her Sa_{O_2} was 100% with an ET_{CO_2} of 45 mm Hg. After tracheal extubation, the Sa_{O_2} declined to 49% over the next 2 min in spite of a jaw thrust maneuver, the insertion of a nasopharyngeal airway, and attempts at positive pressure ventilation. A 7.0-mm inner diameter tracheal tube was inserted transorally without visualization of the vocal cords. No CO_2 waveform was seen on the capnograph, only a flat line. However, before removing the tracheal tube, the Sa_{O_2} rapidly rose to 100% and the patient's color improved. It was subsequently found that a mucous plug had occluded the sampling catheter going to the capnograph. On replacing the capnograph sampling tube, a normal capnograph waveform was seen.

Discussion. This case documents the difficulties involved in differentiating between esophageal and tracheal tube placement when the larynx has not been visualized. It has even been noted that nondecreasing CO_2 waveforms can be observed by capnography after esophageal tube placement (3). The present case illustrates that, because of equipment failure, a previously functioning capnograph showed no $ETco_2$ after correct tracheal tube placement. It has been suggested (4) that preoxygenation be omitted before tracheal intubation so that cyanosis or desaturation will quickly be noted if esophageal intubation occurs. The rapid increase in Sao_2 from 49% to 100% confirmed correct placement of the tracheal tube and demonstrates the value of pulse oximetry in rapid verification of correct position of the tracheal tube in the presence of pronounced oxyhemoglobin desaturation.

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Wound Infiltration and Inguinal Herniorrhaphy

Key Words: PAIN, POSTOPERATIVE.

To the Editor:

We read with interest the paper by Tverskoy and colleagues on postoperative pain after inguinal herniorrhaphy with different types of anesthesia (1). We would like to comment on two aspects of this paper.

To assess the analgesic qualities of the three different anesthetic techniques, the authors used the same dosage regimens of meperidine for each group of patients and compared the resultant pain scores. This has the important advantage of limiting the assessment of pain difference to one index, as opposed to the more common approach using a combination of differences in pain score and consumption of analgesics. To achieve this experimental aim the three patient groups were each prescribed doses of meperidine that we can only consider inadequate with respect to the group of patients who received no perioperative analgesia. The use of patient-controlled analgesia (PCA) systems would have provided advantages for both patients and authors. Many studies have demonstrated the superior analgesic qualities of PCA systems (2,3), and patients normally will titrate their analgesic uptake to achieve an equianalgesic state. The amount of analgesic used is therefore a direct measure of the efficacy of the drug or technique being examined and has been used successfully in this manner (4,5). This would have provided a more objective test of the techniques at issue.

The authors suggest that the long-lasting differences in pain intensity may result from the prevention of intraoperative nocioceptive impulses causing spinal cord hyperexcitability, and that light general anesthetic alone would be insufficient to prevent this. Although this may be true, one would then expect a decreased effect on analgesia if wound infiltration is carried out immediately before wound closure. This has not been demonstrated, and the study by Patel and colleagues (6) suggests that this is not the case. Thus the timing of wound infiltration and its relationship to postoperative analgesia awaits clarification by further well-controlled studies before it can provide support for the above suggestion.

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In Response:

We thank Drs. Trotter and Langton for their response to our article (1). They suggest that the use of PCA as a means of algesimetry would have provided an advantage in our study. We disagree with them for the following reasons. The suggestion that postoperative analgesic consumption adequately reflects pain intensity after surgical operation is only a hypothesis. As indicated by Lehmann (2), conclusive PCA studies to prove this hypothesis are still lacking. Differences in analgesic consumption after different types of surgery (with different severity of postoperative pain) were hardly distinguishable for some opioid drugs used for

PCA (2). Opioid consumption as an index of pain intensity is acceptable, in theory, if there is an adequate opioid concentration-pain intensity relationship that was not yet demonstrated. Austin et al. (3), who studied the relationship between plasma meperidine concentration and postoperative pain intensity, were surprised by the narrowness of the meperidine analgesic concentration range for individuals: After a threshold analgesic concentration is reached, a very small additional increase in the concentration can result in patients' becoming completely analgesic. Another problem with the use of PCA for algesimetry is associated with the development of acute tolerance that may be dependent on the required concentration of an analgesic. In this case, opioid consumption would reflect both pain intensity and degree of the development of acute tolerance.

As far as ethical considerations for patients with a higher pain intensity are concerned, one should consider that, in our patients, constant pain intensity was only between moderate and mild levels. According to Parkhouse et al. (4), who compared the incidence of postoperative pain after various types of surgery, more than half the patients undergoing herniorrhaphy required no postoperative analgesics at all, and one-third required only one injection of an opioid.

We also disagree with the authors' interpretation of the results of the study by Patel et al. (5). Patel and associates reported that severity of postoperative pain is decreased if the wound infiltration with a local anesthetic is carried out immediately before wound closure; there was no comparison of this effect with that of the infiltration made immediately before the incision. We demonstrated (1) that with local anesthesia administered before surgery (effect for 9 h), pain 48 h after the surgery is less severe than with spinal anesthesia (effect for 3 h). This difference might indicate that spinal cord hyperexcitability is caused not only by the nociceptive impulses generated during surgery but also in the immediate postoperative period (the action of proteolytic and inflammatory agents released into wound tissues).

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A Device for Endobronchial Blocker Placement During One-Lung Anesthesia

Key Words: ANESTHETIC TECHNIQUES, ENDOBRONCHIAL—blocker. EQUIPMENT, ENDOBRONCHIAL BLOCKER.

To the Editor:

Fogarty embolectomy catheters can be used as endobronchial blockers for one-lung anesthesia (1,2). Typically, the Fogarty catheter is either inserted into the trachea before intubation with a single-lumen endotracheal tube (2) or alongside the tube after intubation (1).

Placement of the Fogarty catheter can be greatly facilitated by use of the following apparatus (see Figure 1). Two elbow connectors with self-sealing diaphragms are connected in series with the anesthesia circuit attached to the proximal end of the connectors. The distal end of the elbow connectors is then connected to the patient's single-lumen endotracheal tube. The Fogarty catheter can be easily introduced through the diaphragm of one of the elbow connectors while the other diaphragm allows insertion of a fiberoptic bronchoscope that is used to verify correct placement of the catheter in the left mainstem bronchus.

Although our experience with this apparatus has been limited to only two patients, we found proper placement of the Fogarty catheter to be quite easy on both occasions. There were no complications with this device in either patient. However, the Fogarty catheter does create additional potential sites for disconnections and leaks in the breathing circuit.

A special endotracheal tube allowing the use of an endobronchial blocker is commercially available (3) and is useful in elective situations. The above-described apparatus is particularly useful when an intubated trauma patient

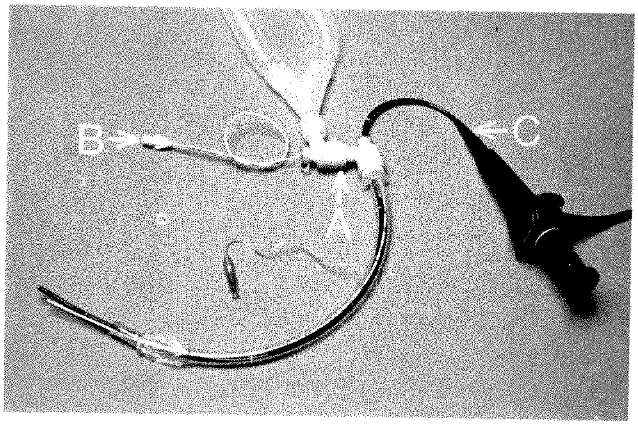

Figure 1. Two elbow connectors (A) are shown interposed between the anesthesia circuit and the endotracheal tube with a Fogarty catheter (B) inserted through one self-sealing diaphragm and a fiberoptic bronchoscope (C) inserted through the other self-sealing diaphragm.

with facial and/or neck injuries requires one-lung anesthesia for emergency thoracic aortic repair. The patient's neck does not have to be manipulated and the airway remains secure while one-lung ventilation is implemented.

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Anesthesia for Zenker's Diverticulum

Key Words: GASTROINTESTINAL TRACT, ESOPHAGUS—Zenker's diverticulum.

To the Editor:

We read with interest the case report of Thiagarajah et al. (1) and their excellent discussion of the anesthetic management of patients with Zenker's diverticulum. We believe, however, that a number of points were made that would benefit from further attention.

We must agree that the most important measures for preventing regurgitation from the pouch are preoperative emptying by external pressure and head-up tilt at the time of induction of anesthesia. We believe that the importance of smooth induction of anesthesia, with no coughing, straining, or gagging, must also be stressed. Coughing and straining, which will apply external pressure to the pouch causing possible regurgitation, are easily provoked during the application of local anesthetics before awake intubation. In view of this, we would argue that awake intubation, which could lead to regurgitation in the presence of partially obtunded airway reflexes, may not be the best technique to choose for these cases.

Cricoid pressure may be contraindicated in patients with a pharyngeal pouch. To decide if it will be harmful or beneficial requires careful review of the barium swallow films by someone expert in interpreting such films. If there is any doubt or if the films are not available, cricoid pressure should not be used.

Finally, should succinylcholine be used in these patients, inasmuch as by causing muscle fasiculation it may cause compression of the pouch? In our experience premedication with papaveretum and hyoscine followed by intravenous administration of a short-acting barbiturate and a nondepolarizing muscle relaxant, with gentle ventilation of the patient using nitrous oxide and oxygen, results in smooth induction of anesthesia. This technique when combined with preoperative emptying of the pouch and head-up tilt may be the safest choice.

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Continuous Alfentanil Infusion for Stereotactic Brain Biopsy

Key Words: ANESTHESIA, NEUROSURGICAL—stereotaxis. SURGERY, NEURO—stereotaxis.

To the Editor:

We read with interest the article by Connelly and Weinstock (1) describing continuous alfentanil infusion for extracorporeal shock wave lithotripsy. We would like to report the use of this technique in patients undergoing stereotactic brain biopsy.

The combination of computed tomography with stereotactic instrumentation has changed some indications for craniotomy (2). In a patient with an intracranial mass lesion, stereotactic biopsy is used to obtain a tissue diagnosis so that further treatment can be appropriately planned, avoiding an initial, diagnostic craniotomy (3). A computed tomography (CT)-compatible head holder (stereotactic head-frame) is fixed to the patient's head in the operating room, under either general anesthesia or, more commonly, intravenous sedation and local anesthesia. Significant anesthesia is required, as the procedure entails creation of holes in the scalp, drilling through the outer table of the skull, and driving four supporting pins into the calvarium to provide absolute immobility of the circular head-frame. The patient is then transferred to the CT suite, where stereotactic coordinates of the lesion related to the position of the head-frame are obtained from CT scan. After the scan, the archived data tape is entered into a compatible operating room computer system for stereotactic coordinate calculation. Then, using these coordinates, a hole is drilled through the calvarium and a biopsy needle is advanced to the calculated depth.

Intravenous sedation is the most common method of anesthesia used for stereotactic brain biopsy at our institution. Disadvantages of this method include risk of respiratory depression and an uncooperative patient secondary to inadequate pain control. In our experience intubation of the patient with a head-frame in place is very difficult, despite normal anatomy, because of severely limited head extension. A small "gate" is present anteriorly for laryngoscopy but is often inadequate for manipulation of a laryngoscope handle. For this reason, we always have fiberoptic equipment on standby for immediate use if necessary. General anesthesia has been used in the anesthetic management of patients undergoing stereotactic brain biopsy (2), but transport of anesthetized patients to the CT suite requires even more extensive equipment and monitoring. Additionally, patients must remain intubated while waiting for CT scan data to be transferred to the operating room computer system, which significantly prolongs the duration of anesthesia.

A continuous infusion of alfentanil supplemented by 1.25–2.5 mg of droperidol and 1–2 mg of midazolam has been used for approximately 20 patients undergoing stereotactic brain biopsy at our institution. Patients received a loading dose of 5 μg/kg of alfentanil followed by alfentanil infusion of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the placement of the head-frame. The infusion was stopped before transfer to the CT suite. Patients received a repeat bolus of 5 μg/kg of alfentanil on return to the operating room and the infusion was restarted at the previous rate. We did not detect any evidence of chest wall rigidity, apnea, or hypoxia and, based on postoperative interviews, patients have been comfortable intraoperatively. Stable hemodynamic parameters have also supported our use of this method.

Because of the direct relationship between Pa_{CO_2} and intracranial pressure, respiratory depression in the majority of neurosurgical patients is a critical issue. Continuous alfentanil infusion has been used previously for awake craniotomy for resection of epileptogenic foci (4). Welling and Donegan reported an increase in Pa_{CO_2} from 38 to 54 mm Hg in a patient given 2.5 mg droperidol, 20 μg/kg alfentanil (in four divided doses), and an alfentanil infusion started at 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. We found that smaller doses of alfentanil were sufficient to keep our patients comfortable during stereotactic brain biopsy, which in contrast, does not require sawing of the calvarium or the turning of a bone flap. We did not measure arterial blood gas tensions, but continuously monitored hemoglobin saturation by pulse oximetry and none of our patients had worsening of their neurologic status postoperatively.

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When Sympathectomy Fails to Relieve Causalgic Burning Pain

Key Words: PAIN, CAUSALGIA. SYMPATHETIC NERVOUS SYSTEM, REFLEX DYSTROPHY—causalgia.

To the Editor:

An interesting case of causalgia was presented by Cicala and associates (1), one distinguished by incomplete relief of lower extremity causalgic pain by lumbar sympathetic block, in contrast to apparently complete relief with continuous epidural anesthesia. In this case, it was observed that sympathetic blockade at L-2 and L-4 relieved hyperesthesia (stimulus-evoked pain) and erythema, but that the spontaneous burning pain was not relieved. On the other hand, epidural blockade was able to relieve all these symptoms. This case, as well as the following cases below, demonstrates that sympathectomy alone may not always relieve all the components of causalgic pain.

Hopkins and Charters (2) also presented a case in which a patient with lower extremity causalgia experienced relief of stimulus-evoked pain (allodynia) after lumbar sympathetic block, but his spontaneous causalgic burning pain persisted. Loh and Nathan, in their report on 45 patients (3), also noted that when hyperpathia and hyperesthesia (forms of stimulus-evoked pain) were relieved by sympathetic blockade, the spontaneous burning pain was not always relieved. Hoffert and associates (4), on the other hand, described a patient in whom lumbar sympathectomy on two separate occasions relieved spontaneous burning pain in a case of lower-extremity causalgia but failed to relieve stimulus-evoked pain (allodynia)—the latter required sensorineural blockade (sural nerve) for relief.

If sympathectomy (whether local anesthetic ganglion block or intravenous regional block) fails to produce the desired pain relief, continuous sensorineural blocking techniques such as the epidural infusion described by Cicala may be efficacious in providing combined sensory and sympathetic blockade. This can immensely facilitate physical therapy and weaning from narcotic analgesics. An alternative to the epidural infusion is the continuous lumbar plexus block favored by Parkinson (cited in Reference 5), and for upper extremity pain the various approaches to continuous blockade of the brachial plexus (reviewed in Reference 5) may be employed. It is beyond the scope of this discussion, but a host of other approaches (6), including oral medications, transcutaneous electrical nerve stimulation, and biofeedback, may be appropriate. The basic message is that there are potentially useful alternatives to sympathectomy if the initial sympathetic block has failed to relieve all of the pain.

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Neuropathic Pain May Not Respond to Sympathetic Blockade

Key Words: PAIN, CAUSALGIA. SYMPATHETIC NERVOUS SYSTEM, REFLEX DYSTROPHY—causalgia.

To the Editor:

An amplifying comment on the clinical report by Cicala et al. (1) is called for. I believe that the patient's presenting problem (pain after lumbosacral plexus injury) may have been more complex than just "causalgia," with two separate identifiable components, namely reflex sympathetic dystrophy plus lumbosacral plexopathy or S2 radiculopathy, or both.

This seems to be borne out by resolution of peripheral symptoms—other than burning neuropathic pain—with lumbar sympathetic block, and resolution of both pain complaints by caudal block.

I have no quarrel whatsoever with the choice of procedure and the gratifying outcome, but rather with the implication of the title (i.e., causalgic pain . . . does not respond to sympathetic block), which may not be telling the complete story. The continuous epidural block—rather than just obliterating causalgic pain—may have killed two birds with one stone. That is, sympathetic blockade to reverse reflex sympathetic dystrophy, plus lumbosacral root block (proximal to the presacral site of neural injury) to alleviate deafferentation pain.

Good treatment outcome, but the pain problem perhaps may have been more complex than intimated by the title.

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Reference

1. Cicala RS, Jones JW, Westbrook LL. Causalgic pain responding to epidural but not to sympathetic nerve blockade. Anesth Analg 1990;70:218–9.

In Response:

As Dr. de Jong points out, it is impossible to be absolutely sure of the diagnosis of causalgia in a case such as we described. A pain problem of this nature is quite complex, and seems to fall through the cracks of diagnostic terminology. Certainly the idea Dr. de Jong puts forth, that the patient suffered both from sympathetically mediated pain and from deafferentation pain secondary to his lumbar plexus injury, is worth consideration. This patient was pain-free for more than 3 wk after injury, however, which possibly eliminates deafferentation pain as a major causative factor.

As we stated in our report, this case was complex diagnostically, and the possibility of misdiagnosis of causalgia must be entertained. For lack of a better category, however, we believe that patients with severe burning pain, hyperesthesia, and vasomotor and sudomotor changes should be diagnostically classed as having sympathetically mediated pain. If this pain is accompanied by a nerve injury, the diagnosis of causalgia seems most likely and appropriate.

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Book Reviews

Smith's Anesthesia for Infants and Children

Etsuro K. Motoyama and Peter J. Davis, eds. St. Louis, Missouri: C. V. Mosby Company, 1990, 948 pp, $89.00.

In the past 20 years the subspeciality of pediatric anesthesia has advanced from the practice of a small group of anesthesiologists to a major scientific subdiscipline of anesthesia. There has been a concomitant increase in the understanding of the physiologic differences of infants and children and in the techniques of providing anesthetic care for them. A similar growth in the field can be seen in the history of *Smith's Anesthesia for Infants and Children.* Although the first four editions of this book were written for the most part by Robert M. Smith, this edition has grown to be a multiauthored text, edited by two leading workers in the field.

The editors state in the preface that the purpose of the book is "to provide a comprehensive presentation of physiology and clinical anesthetic care of infants and children for the use of practitioners at all levels of experience." This reviewer believes that the authors have nobly carried on the tradition of Robert Smith and have produced a textbook that is valuable as a reference for both the practicing pediatric anesthesiologist and the occasional pediatric anesthesiologist faced with an unusual problem.

The book is divided into four major parts: basic principles in pediatric anesthesia, general approach to pediatric anesthesia, clinical management of special surgical problems, and associated problems in pediatric anesthesia.

The part dealing with basic principles in pediatric anesthesia reviews important aspects of the care of patients, differences between adults and children, pediatric respiratory and cardiovascular physiology, management of fluids and electrolytes, and temperature regulation and pharmacology. The part on the general approach to pediatric anesthesia deals with issues such as preoperative preparation, induction of anesthesia, endotracheal intubation, intraoperative management, and specialized areas such as hypotensive anesthesia, blood conservation, and regional anesthesia. Under clinical management of special surgical problems, the editors have grouped discussions of neonatal anesthesia, and of thoracic, neurosurgical, and other subspeciality areas within pediatric anesthesia. Finally, under associated problems in pediatric anesthesia, there are discussions of malignant hyperthermia, concomitant systemic disorders, intensive care, safety, and medical/legal aspects of pediatric anesthesia.

In general, the chapters are excellent reviews that present sound physiologic information supported by numerous references. The clinical information is helpful, and there is a discussion of many of the recent changes in the approach to pediatric anesthesia, such as having parents present during the induction of anesthesia. The illustrations are generally well done, and this reviewer was made right at home by seeing some illustrations from previous editions.

Especially helpful are a number of appendices at the end of the book including information on drug doses, prophylaxis of bacterial endocarditis, growth curves, normal values for pulmonary function tests, and an index of syndromes with their anesthetic implications.

It is unfortunate that, given the rapidly growing interest in pain management over the past few years, there is not a specific chapter on pain and pain management, but, in fact, the information is in the book, scattered in several different chapters.

This book is very well done and will remain an authoritative reference in pediatric anesthesia. *Smith's Anesthesia for Infants and Children* is recommended to residents, to pediatric anesthesia practitioners, and to the occasional pediatric anesthesiologist. For those looking for a cookbook approach to pediatric anesthesia, however, this book would probably not be satisfactory, as it is quite detailed. This is not the book in which to look for a list of important points in doing, for example, anesthesia for adenoidectomy. Rather, one is provided the background information necessary to formulate an anesthetic plan for a particular patient.

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Anesthesia for Major Vascular Surgery

Michael F. Roizen, ed. New York: Churchill-Livingstone, 1990, 505 pp, $75.00.

This book is composed of six sections subdivided into a total of 31 chapters written by 32 contributors. Essentially,

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all aspects of anesthesia considerations for patients undergoing major vascular surgery are addressed. The style of presentation of the material varies markedly from contributor to contributor and subject to subject. For example, the two chapters on morbidity and mortality are thorough, informative, and written in the classical style. For the most part, they are up to date. One chapter has 122 references, but only one is dated after 1986 and the other is similarly well done with 172 references, a number of them after 1986.

The sections concerning surgery are written by surgeons and are clear and concise yet comprehensive, with the exception of coverage of the use of lasers and atherectomy devices. The chapters concerning anesthetic management of patients are presented in a much different format. The format is more one of "this is how we approach this at my institution." Although the reader is finally able to enjoy an expert committing himself to a specific plan of action he or she is also exposed to personal bias that has a tendency to creep into the presentation and discussion. This latter point is evidenced by the fact that regional anesthesia for carotid endarterectomy is covered only in passing or is discounted in three chapters. There is also a great deal of redundancy of material when three separate chapters on the same topic are presented in a "how we do it" fashion from the University of Chicago, the Mayo Clinic, and Stanford. A "how we do it" approach is often not as balanced and as thorough as a more conventional approach and to a degree that is true of these chapters.

Conversely, this style of presentation can be reviewed as a strength in that the reader is aware that similar approaches, concerns, and considerations are embraced by three different experts at three separate institutions. However, it may also have added spice to the controversy to have had one of the chapters written by someone who preferred regional anesthesia as a primary choice. One of Dr. Roizen's unique strengths is the ability to break monitoring down into an equation of cost-effectiveness and we are not disappointed with his chapters in this text.

There are a number of controversial statements made in various chapters such as "a CVP catheter is very useful in virtually all patients undergoing carotid endarterectomy" (Larson), a retrospective analysis of 2000 patients clearly demonstrating isoflurane as the most protective volatile agent (Michenfelder, not referenced, no outcome data), and "we believe that if general anesthesia is the safest for these cases—it seems reasonable to assume that general anesthesia would be the safest choice for all cases" (Michenfelder, repeated by Roizen).

The chapters concerning anesthesia for emergent surgery are fairly redundant and could easily be incorporated into other chapters. Much of the chapter concerning visceral ischemia could have been absorbed into the chapters on carotid and aortic vascular surgery. As with many of the chapters earlier in the text, discussions of general evaluation of patients undergoing aortic surgery are similar in scope and depth to the evaluation of a patient undergoing carotid surgery. Possibly a specific chapter with special reference to individual surgical procedures and anesthetic techniques may have been more useful and less redundant.

This reviewer found one of the strengths of the text to be Section 6, which deals with controversies. The sections on electroencephalography and evoked potential monitoring are clear and instructive. The controversy surrounding the use of pulmonary artery catheters is addressed in an insightful manner despite the use of the trade name Swan-Ganz, and the chapter concerning echocardiography is equally well done. The chapter concerning anticoagulation could have easily been expanded; that on blood transfusion is both comprehensive and useful. The final chapter is one of the best written on the subject. A schematic presentation on the sequence and decision making when ordering coagulation studies to evaluate the bleeding patient would have been useful. Aprotinin is not mentioned and DDAVP (desmopressin) is only mentioned in passing.

In summary, this text, like most others, has a mixture of excellent chapters and some that fall short of the mark. In general, the book offers a wealth of material concerning vascular anesthesia compiled into a single source; however, in this reveiwer's opinion the book falls short of being a single source of information on the subject and other source material will be required for a comprehensive coverage of many topics. This text is recommended to anesthesia residents and to anesthesia departments as an addition to their libraries.

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Mastering Infrared Capnography

Z. Kalenda. Zeist, The Netherlands: Kerckebosch, 1989, 267 pp, $114.85.

The use of capnography has rightfully become ubiquitous in the practice of anesthesiology. The complexity of the technology of capnography is often underestimated, leading to misapplication and misinterpretation of results. A monograph describing the basic principles of capnography would form a basis for more rational application of this exciting technology. Unfortunately, Professor Kalenda's book does not fill this need.

The purpose of the text is ostensibly to give the reader an understanding of the basic principles and applications of infrared capnography. The book is divided into six sections: a foreword, "CO_2—Physiological Aspects," "Infrared CO_2 Analyzers," "Examples of Clinical Application," "Multiple Monitoring," and "The Study and Storing of Monitoring Records."

Each page consists of a large illustration or algorithm, followed by not more than a few paragraphs of text. Many of the figures are quite simplistic and seem to be more suitable as slides for a lecture than as illustrations for a text. Additionally, many of the figures are redundant.

There is a simplistic explanation of the physics of absorption spectroscopy and the basic mechanics of different sampling systems for respiratory gas analyzers, but a more sophisticated treatment of these topics is missing. The distortion of the capnography waveform by sampling systems and the resulting errors in the estimation of actual CO_2 content are given superficial coverage. The much more difficult question of the relationship between true end-tidal gas concentrations and the alveolar and arterial concentrations is barely approached.

Entire chapters have only tenuous relation to the book's theme. A chapter entitled "Multiple Monitoring" is a compendium of capnograms (along with electrocardiograms, arterial blood pressure recordings, and a plethysmogram from an unidentified site) showing irregular breathing in a patient with trigeminal neuralgia. The relevance of this chapter escapes the reviewers. The chapter entitled "The Study and Storing of Monitoring Records" consists merely of a photograph of two men studying a long paper record, a photograph of a microfilm reader, a photograph of a microfilm camera, and a few simple block diagrams concerning electronic storage media. Each figure takes up about a page.

This book is of use neither to the beginner who seeks a fundamental grounding in the basic principles of infrared capnography, nor to the more advanced student who seeks a rigorous treatment of the subject. Some of the diagrams may be of use to those needing to make slides for lectures. Readers desiring an introduction to the principles of capnography are referred to the appropriate chapters in Blitt's text, "Monitoring in Anesthesia and Critical Care Medicine" (New York: Churchill-Livingstone, 1985).

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The Pain Clinic Manual

Stephen E. Abram, ed. Philadelphia: J.B. Lippincott,
1990, 458 pp, $29.50.

Anyone looking for a basic panoramic review of Pain Clinic practice need look no further. *The Pain Clinic Manual* is the right book. In a relatively slim (by medical textbook standards) volume (316 pp, plus appendices and index), this book presents a compendium of experience in a clear and easy-to-read style. Sixteen contributors from the Medical College of Wisconsin include a family practitioner, oncologist, radiotherapist, physiotherapist, psychologist, psychiatrist, and several anesthesiologists. They bring their own expertise to the now classic feature, "The Pain Clinic." This manual provides a series of well-organized, concise and straight-to-the-point remarks that reflect a consensus on the management of chronic pain. As the Preface warns, this is "by no means a definitive reference," which would have to be ten times longer.

The manual begins by reviewing the inner workings of a multifaceted organization and presents an ideal physical layout of a pain clinic. Anesthesiologists are said to be best equipped to manage posttraumatic pain problems, although one can argue that their role is definitely expanding in the management of cancer pain. Pain pathways and mechanisms are very superficially exposed, but references succeeding each chapter allow the reader to pursue these topics in greater depth. The section on the psychological aspects of pain is, on the other hand, a very useful "reader's digest." The chapter "Primary Patient Evaluation," which includes history, physical and psychological evaluation, diagnostic tests, and procedures, is relatively detailed and can provide a solid base for routine patient care. Pain management is divided into two sections. First, the "Management of Common Nonmalignant Pain Syndromes" describes 14 different entities. Readers may occasionally disagree with the therapeutic choice, which is deliberately simplistic, in complex areas. It is worth repeating the warnings given by the editor, that "treatment suggestions . . . are by no means uniformly effective," that "for most pain syndromes, there is an inverse relationship between the duration of symptoms and the chance of [therapeutic] success," and that "single modality" treatments . . . cost "patients and society dearly, both in financial costs and personal suffering." Second, for the "Management of Common Cancer Pain Syndromes" the pharmacological treatment follows the now widely accepted "analgesic ladder" concept publicized by the Cancer Pain Relief Program of the World Health Organization. The review of interventional treatment modalities is somewhat disappointing, from intraspinal narcotic techniques (which are not sufficiently developed, at a time when they are becoming rapidly a major treatment modality) to dorsum column stimulation (dismissed as ineffective, while an increasing number of anesthesiologists are, with some success, working to improve the technique). The reader does not come away with the impression of the rapid evolution occurring in this field, where the demand for improved patient care is great and where the anesthesiologist is playing an increasingly important role.

This last remark emphasizes a major change over the last few years as the role of the anesthesiologist in management of pain has expanded to include the field of acute pain, especially postoperative pain. More specifically, it is regrettable that this manual does not mention the necessary expansion of the Pain Clinic and of the number of physicians (i.e., mostly anesthesiologists) involved in its function.

It remains, however, that this very well-written and easy-to-read book will be an invaluable "primer" for all trainees who rotate in the Pain Clinic. Questionnaires and checklists included in the appendix will also be extremely helpful for practitioners dealing with chronic pain. This is a very useful "guide" that, to keep its value, will need to be frequently updated to keep pace with the rapid evolution of its subject.

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Preoperative Cardiac Assessment

D. T. Mangano, ed. Philadelphia: Lippincott, 1990, 174 pp, $38.00.

Preoperative cardiac assessment must mean different things to different people. In the preface, the editor promises to discuss preoperative assessment strategies. This reviewer expected help in one or more of the following areas: (a) clues to look for in the history, physical, and routine preoperative tests that may indicate undiagnosed cardiac disease; (b) advice on the right questions to get the most out of a cardiology consult; (c) a perspective on the clinical significance of the results of the myriad of tests that cardiologists order; (d) discussion of the relationship between the severity of disease and the risk to the patient of the proposed anesthesia, surgery, and convalescence; and (e) some insight into the decision to proceed with or to postpone elective surgery. Unfortunately, lack of focus on the book's theme resulted in difficulty finding information on these very points.

The first chapter, "Preoperative Assessment of the Patient With Ischemic Heart Disease," clearly describes most of the available tests for ischemia and left ventricular dysfunction and presents some of the difficulties in interpreting them. Significantly, a discussion of 24-hour electrocardiogram monitoring is omitted. Absent, too, are discussions of the very important concepts of the effect of pretest probability of disease on posttest probability of disease and of the clinical significance of disease probability between 10% and 90%. No algorithms are presented to help the anesthesiologist understand what the cardiologist might be considering, nor are there any to help the anesthesiologist decide whether a cardiology consult is necessary in the first place.

Chapter 2, "The Patient With Valvular Heart Disease," assumes that the diagnosis of valvular heart disease has been made. The preoperative assessment strategies are buried in admittedly excellent physiologic discussions and must be exhumed by the reader. Nowhere are there direct statements such as, "in patients with mitral stenosis important preoperative considerations are . . . ." Missing are tables and patient preparation algorithms to help direct the clinician. A stronger discussion of perioperative anticoagulation in patients with valvular prostheses would also have been appreciated.

Chapters 3, 4, and 5 are organized more in keeping with the reviewer's interpretation of the title. In chapter 3, "The Patient With Congenital Heart Disease," the tables of risk factors before and after repair or palliation are very helpful. However, there are too many "you should . . ." statements without direct explanation of *why* you should. Chapter 4, "Preoperative Assessment of the Patient Undergoing Noncardiac Thoracic Surgery," is a well-focused discussion of the preoperative pulmonary assessment of patients presenting either for nonthoracic surgery or for noncardiac thoracic surgery. Table 4-1 covers a totally unrelated topic. Chapter 5, "Preoperative Cardiac Medications," is well organized. This reviewer had hoped the tradition of stopping diuretics preoperatively in patients with compensated congestive failure would have been challenged. It would also have been interesting to have included discussions evaluating the effectiveness of the chronic medication, the potential need to supplement preoperatively, and the problems associated with converting oral drug regimens to intravenous ones.

This book fell short of expectations from these distinguished authors. The criticism is not that the information presented is wrong or that the chapters are not worth reading—they all are. However, the information in chapters 1, 2, and perhaps 3 does not focus directly on clinical questions that arise in the preoperative cardiac evaluation.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Beach TR. *Specialty Board Review: Anesthesiology*, 3rd ed. East Norwalk, Conn.: Appleton & Lange, 1990, 305 pp, $35.95.

Cucchiara RF, Michenfelder JD. *Clinical Neuroanesthesia*. New York: Churchill Livingstone, 1990, 555 pp, $79.00.

Gorback MS, ed. *Emergency Airway Management*. Philadelphia: B. C. Decker, 1990, 183 pp, $29.95.

Gregory GA, ed. *Pediatric Anesthesia*, 2nd ed. New York: Churchill Livingstone, 1989, 1388 pp, $125.00.

Kirby RR, Banner MJ, Downs JB, eds. *Clinical Applications of Ventilatory Support*. New York: Churchill Livingstone, 1990, 546 pp, $69.95.

Tufte ER. *Envisioning Information*. Chesire, Conn.: Graphics Press, 1990, 126 pp, $48.00.

White PF, ed. *Outpatient Anesthesia*. New York: Churchill Livingstone, 1990, 520 pp, $65.00.

Yeager MP, Glass DD, eds. *Anesthesiology and Vascular Surgery. Perioperative Management of the Vascular Surgical Patient*. East Norwalk, Conn.: Appleton & Lange, 1990, 379 pp, $69.95.

Zahl K, Meltzer MA, ed. *Regional Anesthesia for Intraocular Surgery*. Ophthalmology Clinics of North America, Volume 3, No. 1. Philadelphia: W.B. Saunders, 1990, 129 pp, $76.00 annual subscription for four issues.

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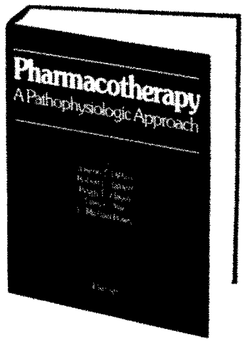

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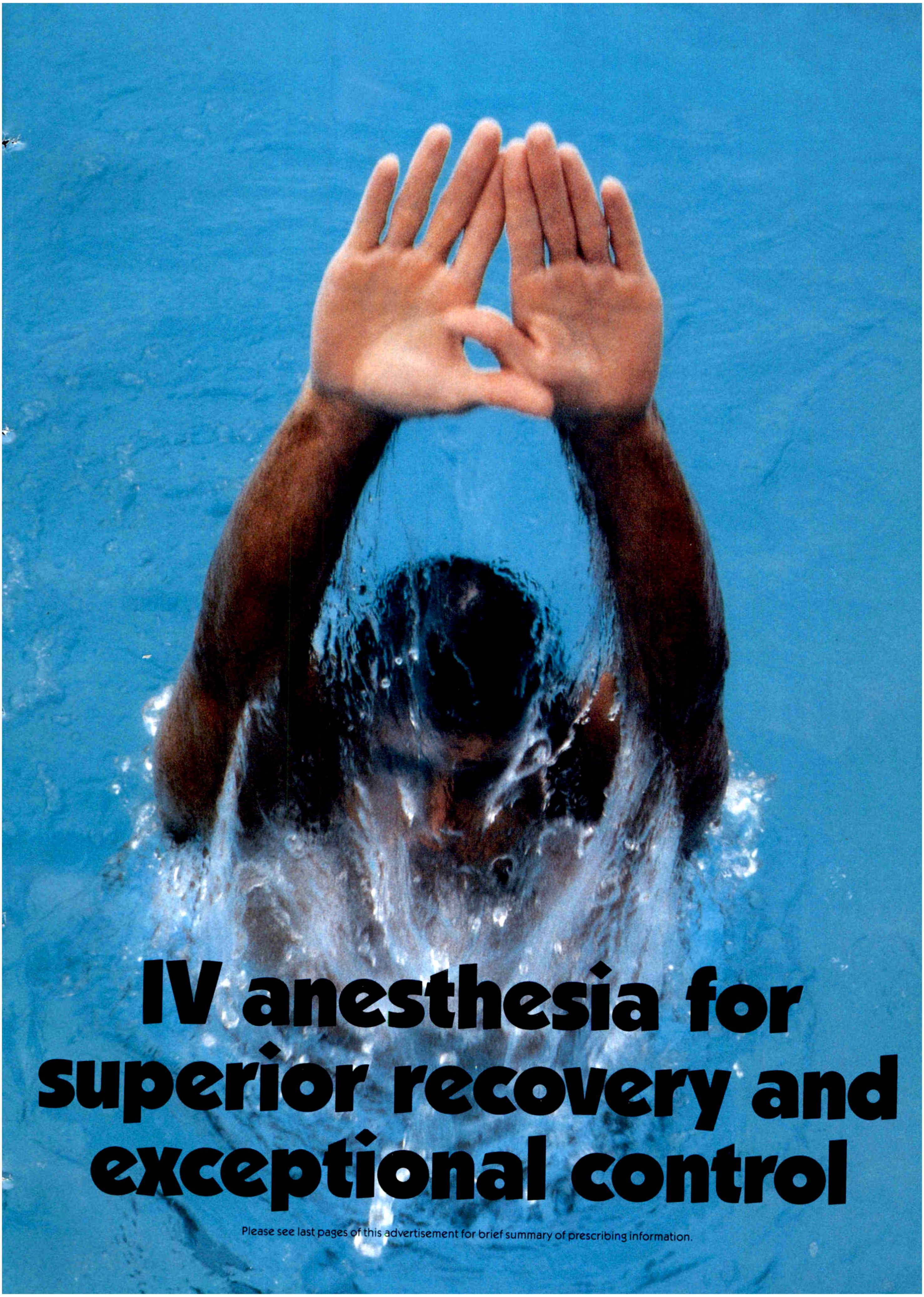

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—adapted from Korttila et al, p A564[1]

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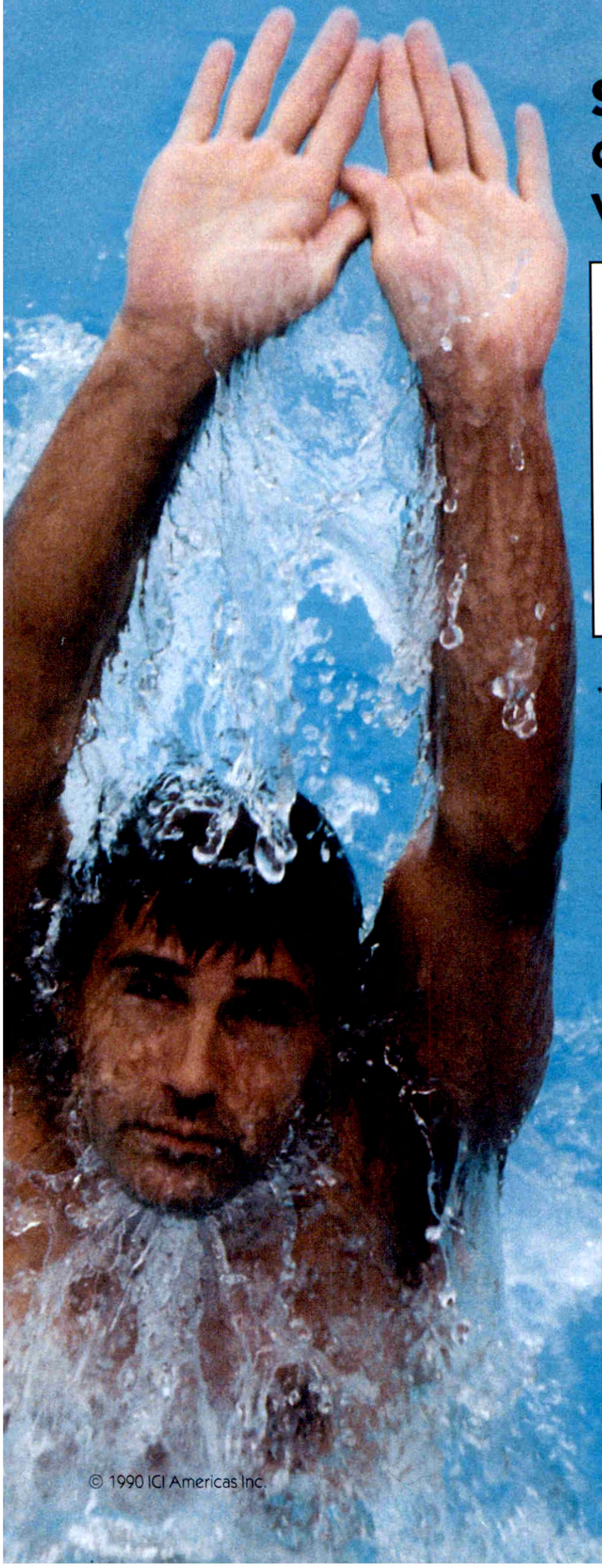

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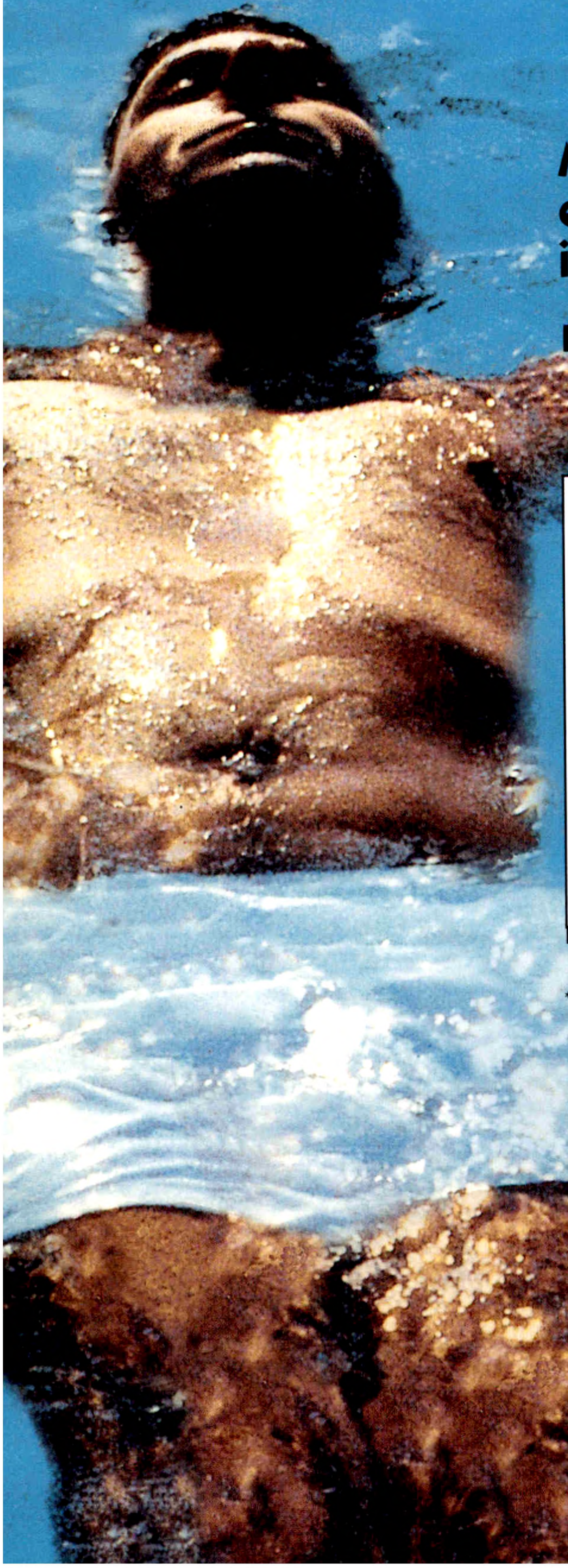

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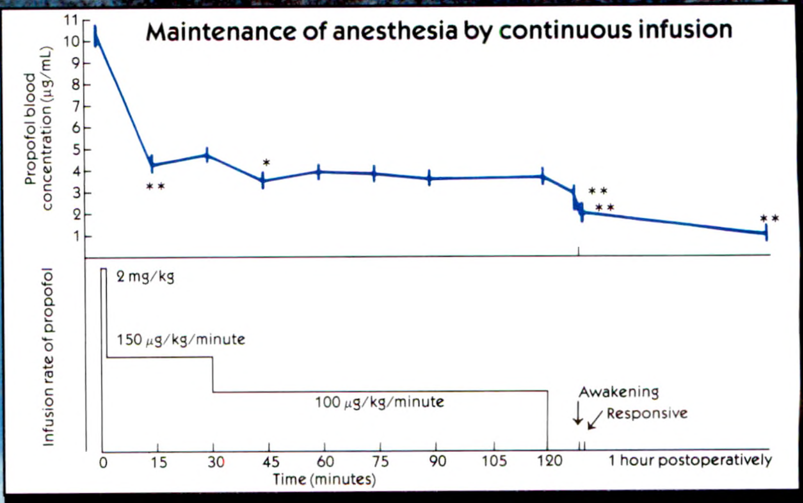

—adapted from Herregods et al, p 364[4]

*Significant difference (*P* < .05) from previous value.
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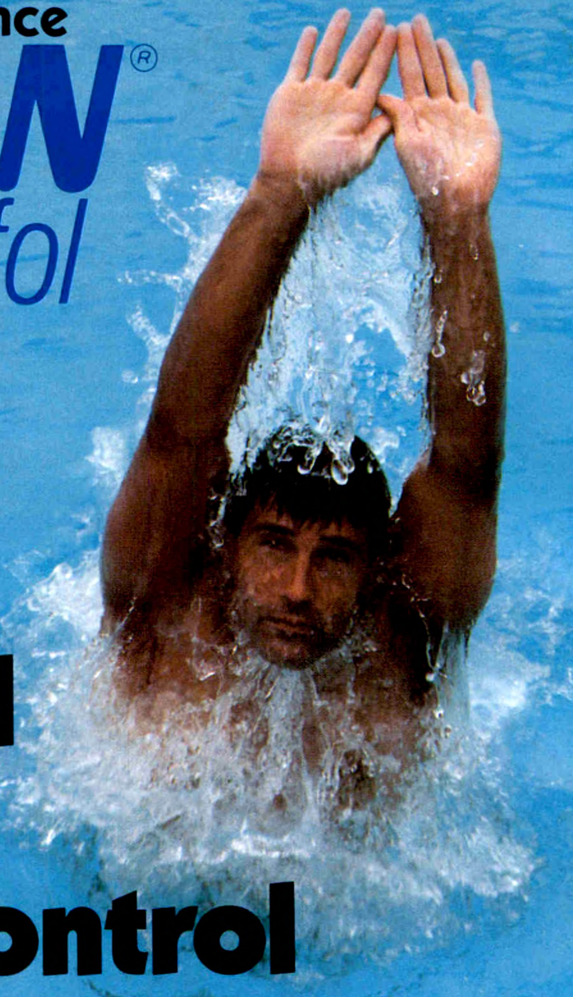
Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®
INJECTION
propofol



For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. 2. Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 3. Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. 4. Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. 5. Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.

STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN®

JECTION
mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

full prescribing information, see package insert.)

ATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction r maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.
PRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there nsufficient data to support its safety to the fetus. (See PRECAUTIONS.)
IPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been rted to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not wn. (See PRECAUTIONS.)
PRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have been established. (See PRECAUTIONS.)
IPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure npaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial ssure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)
TRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity DIPRIVAN Injection or its components.
ARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is ndicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the ecovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother s probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-ontrolled studies in pregnant women. Because animal reproduction studies are not always predictive of human esponses, this drug should be used during pregnancy only if clearly needed.

abor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, ecause there are insufficient data to support its safety to the fetus.

ursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has een reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are ot known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials
Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.
Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)
Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)
Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.
– 5% Dextrose Injection, USP
– Lactated Ringers Injection, USP
– Lactated Ringers and 5% Dextrose Injection
– 5% Dextrose and 0.45% Sodium Chloride Injection, USP
– 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Rev. X 06/90

Made in Sweden
Manufactured for:
STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

Classified Advertising

NEW HAMPSHIRE

Opening for board-certified anesthesiologist to join four MDs and six CRNAs in 190-bed modern community hospital. All types of surgery except cardiac. Moderate obstetrics. Must be energetic and good with epidurals and invasive lines. Excellent fringe benefits and early partnership. One hour drive to seacoast, ski resorts, and Boston. Send CV to Prospect Anesthesia Services, P.C., 10 Prospect Street, Nashua, NH 03060.

419E/J

ANESTHESIOLOGY RESIDENCY POSITIONS

Electronic Bulletin Board listing available. Residency positions for CA-1 through CA-3 and fellowship years in anesthesiology. Use telecommunication software on a computer (300 or 1200 baud, 8 data bits, 1 stop bit, no parity) to call (716) 473-4246, answer "yes" to the first question, and then follow the menus. This is a service provided by the Association of Anesthesiology Program Directors and the Department of Anesthesiology at the University of Rochester, Rochester, New York.

424F/L

ANESTHESIOLOGIST

Board certified/board eligible, to join a four-member incorporated group with CRNAs, 420-bed community hospital with 7000 cases per year in western Pennsylvania, close to large metropolitan areas. Excellent schools, recreational facilities, friendly community. All types of anesthesia with minimal OB. Reply to Box 428. Fellowship or experience in cardiac anesthesia preferred.

428F/I

UNIVERSITY OF ARIZONA

Expanding University program creates exciting opportunities for new faculty, both academic (tenure) and clinical tracks. Applicants must be interested in academic career. Interested particularly in cardiac, obstetric, ICU, and pediatric subspecialties. An AA/EOE. Contact Burnell R. Brown, Jr., MD, PhD, Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ 85724. Closing date: 12/31/90 or until position is filled.

434F/I

TENNESSEE

Anesthesiologist: Periodically full-time positions become available at the level of Instructor/Assistant Professor. Applicants must be board certified or in the board process and be interested in resident teaching and clinical research. Tennessee license required. If you would be interested in having your name on file, please reply with curriculum vitae to John T. Chesney, MD, Interim Chairman, Department of Anesthesiology, University of Tennessee Medical Center at Knoxville, 1924 Alcoa Highway, Knoxville, TN 37920. UTMC is an Affirmative Action/Title IX/Section 504 Employer.

436F/L

NEW YORK STATE

Immediate permanent placement opportunities in large and growing MD/CRNA anesthesiology group in western New York state, including Director of OB Anesthesia, Director of Pain Management, and staff anesthesiologist. Major center for head, neck, breast, and neuro surgery; no trauma or neonatal. Affiliated with major university. Competitive salary; partnership option; comprehensive benefit package including malpractice and relocation assistance. Canadian anesthesiologists eligible to work in U.S. within next six months may find this group ideal for relocation. Send your CV, in confidence, to CompHealth Anesthesia Search, 5901 Peachtree Dunwoody Road, #C-65, Atlanta, GA 30328. Or, call Samantha Lloyd at 1-800-354-4050 for details (404-391-9876 in Georgia).

506I

ANESTHESIOLOGIST

BE/BC needed to join three-man group in Midwest. Send inquiries, CV, and references to Box 442 G/I.

442G/I

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA, SAN DIEGO

is recruiting for four faculty positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol driven human studies. The three other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anesthesia. One of the four positions may be tenured track. Otherwise the positions are nontenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in Anesthesiology and a California Medical License is required. Possession of a certificate of special qualifications in Critical Care Medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego, is an Equal Opportunity/AA Employer. All applications received by October 31, 1990 will receive thorough consideration.

445G/I

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum 1/4 page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 633-3853.

Rates. Ads cost $1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia* Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity/affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

446G/L

ANESTHESIOLOGIST
Two BE/BC to join rapidly growing practice in Mobile, Alabama. Early partnership, competitive starting salary. Qualified applicants please send CV to Michael P. Ederer, DO, 3401 Medical Park Drive, Suite 107, Mobile, AL 36693.

447G/I

OREGON
Obstetric Anesthesia: Adding second faculty member at assistant professor level with emphasis on obstetric anesthesia and related research. Will participate in regular OR duties. Experience or training in OB anesthesia required. Required ABA or equivalent certification or must be in ABA exam system. Must be eligible for Oregon license. Send CV and names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

450G/I

BE/BC ANESTHESIOLOGIST
Southwest Pennsylvania, 300-bed, modern community hospital to work with three MDs and CRNAs. Competative starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to Box 454G/I.

454G/I

WISCONSIN
Milwaukee, on Lake Michigan, America's "most livable city" with extensive cultural and recreational opportunities. Opening for clinical BC/BE anesthesiologist at the Medical College of Wisconsin Section of Obstetric Anesthesia. Obstetric Anesthesia fellowship or extensive experience necessary. Position involves at least 50% time spent teaching residents at a large community hospital with level III nursery and > 45% patients with anesthesia department intervention. Patient population is mix of 85% private/15% clinic patients. Other clinical or research time may be spent in Department of Anesthesiology, a 50+ member department that trains residents, fellows, and has an extensive laboratory available. Salary and academic position commensurate with experience. MCW is an equal opportunity employer. Reply with CV to Anita Maitra-D'Cruze, MD, Director of OB Anesthesiology, St. Joseph's Hospital, 5000 West Chambers Street, Milwaukee, WI 53210.

455G/I

OHIO STATE UNIVERSITY, COLUMBUS
The Department of Anesthesiology is recruiting board certified/eligible anesthesiologists as a Director of Ambulatory Surgery with specific training and/or experience in adult outpatient surgery. Responsibilities include management of 40–50 patients per day case load as well as resident teaching, research, and patient care. We are an Affirmative Action/Equal Opportunity Employer. Please send CV to Chairman, Faculty Search Committee Ohio State University Hospitals, Department of Anesthesiology, 410 West 10th Avenue, Columbus, OH 43210.

457G/J

COME TO THE NATION'S CAPITAL
Associated Anesthesiologists Service, P.C. (AAS) is seeking qualified physicians to join its practice. AAS is a private practice anesthesia group providing services to the Washington Hospital Center (WHC), an 871 tertiary care facility in the heart of the District. We perform approximately 17,000 surgical procedures annually including 150 kidney transplants. Washington Heart, a renowned program affiliated with WHC performs 1600 open heart procedures yearly including transplant. New facilities, opened in November 1989, include an 18-room operating suite with laser capability, holding and induction areas, and neurosurgical unit.

Physicians completing their training are welcome. All applicants must be board eligible or board certified and possess or be able to obtain a license to practice in the District of Columbia.

For information, please call Mary Ann Coffey at (301) 589-0931 or FAX or mail your CV to Associated Anesthesiologists Service, P.C., 818 Roeder Road, Suite 409, Silver Spring, MD 20910. FAX (301) 587-9276.

460HI

ANESTHESIOLOGIST
BC/BE to join group of 10 MDs with CRNAs in a large hospital located in a pleasant midwestern community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and OB. Excellent starting salary and benefits package leading to early partnership. Send CV to Associated Anesthesiologists of Toledo, Inc., 2409 Cherry Street, Suite 4, Toledo, OH 43608.

461H/J

ANESTHESIOLOGIST
BC/BE to join small group at a modern community hospital in south central Pennsylvania. All types of anesthesia, including open heart. Close to metropolitan areas, good school systems, recreational facilities; excellent benefits, early partnership. Please send CV. Reply to Box 463H/J.

463H/J

CARDIAC ANESTHESIA FELLOWSHIP
Wake Forest University Medical Center offers a 12-month research fellowship in cardiac anesthesia. Both clinical and animal research opportunities are available. The program is designed for candidates completing a 4-year anesthesiology residency continuum who desire academic careers in cardiothoracic anesthesia. Six months or more of cardiac anesthesia at the CA-3 level is a prerequisite. Individuals who have completed anesthesia training programs in other countries are also encouraged to apply. For further information, please write Glenn P. Gravlee, MD, Head, Section on Cardiothoracic Anesthesia, Wake Forest University Medical Center, 300 South Hawthorne Road, Winston-Salem, NC 27103, AA/EOE.

464H/J

DIRECTOR OF ANESTHESIOLOGY AND STAFF ANESTHESIOLOGIST
Needed for large, profitable MD/CRNA anesthesiology group supporting modern 500-bed hospital affiliated with major university in western New York state. Major center for head, neck, breast, and neuro surgery. Competitive salary, partnership option, and benefit package that includes malpractice and relocation assistance. Small town hospitality with big city amenities; major cultural activities, outdoor recreation facilities, and major professional sports teams in the area. Send your CV, in confidence, to CompHealth Anesthesia Search, 5901 Peachtree Dunwoody Road, #C-65, Atlanta, GA 30328. Or, call Samantha Lloyd at 1-800-354-4050 (404-391-9876 in Georgia).

507I

VERMONT
Second anesthesiologist for growing department in modern, 80-bed, acute care hospital. Fee-for-service practice. Lakeside community close to excellent skiing. Income guarantee. Moving expenses. Send CV to New England Health Search, 63 Forest Avenue, Orono, ME 04473. (207) 866-5680 or (207) 866-5685.

467H/J

LOUISIANA
Anesthesiologist. Board-certified or -eligible anesthesiologist to fill clinical faculty positions at a University Medical Center.

The position responsibilities include administration of anesthesia, teaching of residents, and supervision of CRNAs. Encouragement will be given to initiate or participate in research. Faculty rank and salary will be commensurate with experience. Louisiana State University Medical Center, School of Medicine in Shreveport is an affirmative action/equal opportunity employer. Send curriculum vitae to D. Richard Davis II, MD, Chairman, Department of Anesthesiology, LSU Medical Center, P.O. Box 33932, Shreveport, LA 71130-3932.

468H/A

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY

The Department of Anesthesiology of the Medical College of Wisconsin is accepting applications for a 12-month fellowship in pediatric anesthesiology beginning January 1, 1991 (all candidates should have completed the CA-3 year). Experience and training will include all aspects of pediatric anesthesiology including cardiac anesthesia and pain management. Opportunity also is provided for clinical research and critical care experience. Inquiries, CV, and references should be sent to Stephen P. Pontus, MD, Section of Pediatric Anesthesiology, Children's Hospital of Wisconsin, P.O. Box 1997, M.S. 735, Milwaukee, WI 53201.

469H/J

SARANAC/LAKE PLACID, NEW YORK

Third anesthesiologist to join well-established, fee-for-service group affiliated with 90-bed, acute care hospital. Four-season recreation area in beautiful Adirondack region. Send CV to New England Health Search, 63 Forest Avenue, Orono, ME 04473 or call (207) 866-5680 or (207) 866-5685.

470H/J

TENNESSEE—ANESTHESIOLOGY

Full-time positions at levels of Instructor to Associate Professor with emphasis on teaching, patient care, and clinical research. Prerequisites are (1) meet Tennessee license requirements and (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send CV, bibliography, and the names of three references to John Zanella, Jr, PhD, MD, Vice Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163.

The University of Tennessee, Memphis is an Equal Employment Opportunity/Title IX Section 504/Affirmative Action Employer.

471H/J

PACIFIC NORTHWEST

Position available for board certified or soon to be board certified anesthesiologist. Send CV and date available to Box 472H/A.

472H/A

UPSTATE NEW YORK

Full-time anesthesiologists BC or BE to fill available position immediately. Diverse case load. No OH. Pain management experience a plus but not required. Excellent salary and health, life, and disability insurance. Salaried first year leading to early partnership. Send CV and three references to Watertown Anesthesia Services, P.C., P.O. Box 779, Watertown, NY 13601, or call (315) 785-6880.

476H/A

OB ANESTHESIA AND PAIN MANAGEMENT SECTION DIRECTORS

Needed for large, profitable MD/CRNA anesthesiology group; also seeking staff anesthesiologist. This growing group services modern 500-bed hospital affiliated with major university in western New York state. Major center for head, neck, breast, and neuro surgery; no trauma or neonatal. Competitive salary, malpractice insurance, relocation assistance, partnership option. Location near Canadian border makes this ideal for Canadian anesthesiologists eligible to work in U.S. within next six months. All inquiries handled with strictest confidence. Send CV to Samantha Lloyd, CompHealth Anesthesia Search, 5901 Peachtree Dunwoody Road, #C-65, Atlanta, GA 30328. Or call Ms. Lloyd at 1-800-354-4050 for more information (404-391-9876 in Georgia).

508I

MINNESOTA

Four-member anesthesiologist group, part of an 80-member multispecialty clinic, is seeking a board certified/eligible anesthesiologist to replace a retiring member. Anesthesia team care provided at secondary referral hospital (no OH) and freestanding surgery center. Candidate with interest in organizing chronic pain therapy would be given particular consideration. West Central Minnesota location affords recreational and outdoor opportunities. Send CV and three current references to Box 443 GIK.

443GIK

CLEVELAND CLINIC

The Department of Cardiothoracic Anesthesia, Cleveland Clinic Foundation is seeking applications from those interested in 6-month or 1-year CA 3/4 subspecialty training. The experience encompasses the perioperative management of over 4000 patients scheduled for all major cardiac and thoracic procedures. Such positions are available in July 1991 or January 1992. Opportunities for clinical research accompany the vast clinical training. Interested candidates should write to Dr. Erik J. Kraenzler, Department of Cardiothoracic Anesthesia, G-3, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195. The Cleveland Clinic Foundation is an Affirmative Action/Equal Opportunity Employer.

452I

POSITION AVAILABLE

Immediate opening for anesthesiologist with expertise in critical care. This position involves administrative and clinical duties along with teaching responsibilities. Academic appointment based on credentials. Contact John E. Mahaffey, MD, Professor and Chairman, Department of Anesthesiology, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425-2207.

479I

ANESTHESIOLOGIST (SHOCK TRAINING/CRITICAL CARE)

Render anesthetics to patients in shock trauma unit subsequent to diagnosis by general surgeon; evaluate patients and manage airway during necessitation phase to determine air capacity and intake into lungs; induction of patient in operating room; prescribe/administer meds for pain management postoperatively in ICU for ventilation. Supervise residents and fellows in trauma. Must hold general medical license (state of Maryland); experience in anesthesiology related to shock trauma. $10,000/month; Job Location/Int: Baltimore, Maryland. Mail copy of ad and resumé to Job Order # 8943855, Department of Economic and Employment Development, 1100 North Eutaw Street, Room 212, Baltimore, MD 21201.

480I

THE GEORGE WASHINGTON UNIVERSITY MEDICAL CENTER

Academic anesthesiologist at Assistant Professor to Associate Professor level. Requirements for all applicants are: DC license, completion of an approved 4-year residency training program, preferably with 1 year optional training in a specialty, research, or teaching. Additional consideration given to candidates having held previous faculty appointments with participation in research activity leading to publication. Salary commensurate with qualifications. Please have CV and two letters of reference sent to Burton S. Epstein, MD, Chairman, Department of Anesthesiology, The George Washington University Medical Center, 901 23rd Street, NW, Washington, DC 20037. George Washington University is an Equal Opportunity/Affirmative Action Employer. Applications will be accepted until the position is filled but no later than December 1, 1990.

481I

INNOVATIVE ANESTHESIA PRACTICE

Change from academics to service created vacancies in large (18K cases/year) community teaching hospital practice. Need broadly competent anesthesiologists to work with creative colleagues, excellent life-style, above average compensation package. Positions for both experienced and new grads. Contact Box 80447, Country Fair Station, Canton, OH 44708.

482I

CARDIOTHORACIC ANESTHESIA FELLOWSHIP

Washington University Medical Center. Applications are being accepted for 6- or 12-month fellowship (CA-4) starting in 1991. Full spectrum of adult cardiothoracic anesthesia including arrhythmia surgery, and active heart and lung transplantation program. Research opportunities are available. Address correspondence with CV and names of three references to Demetrios G. Lappas, MD, Director, Division of Cardiothoracic Anesthesia, Washington University Medical Center, 660 South Euclid Campus Box 8054, St. Louis, MO 63110.

483I/L

CRNA

Opening for CRNA in a 250-bed teaching medical center with significant trauma volume. Located in an "All-American" city of 175,000, 100 miles north of Los Angeles and close to many excellent recreational areas. Compensation and benefits are competitive. Quality of life exceptional. For more information, contact Human Resources, Kern Medical Center, 1830 Flower Street, Bakersfield, CA 93305. (805) 326-2643. FAX (805) 326-2229.

484I

CALIFORNIA

Los Angeles County, Harbor-UCLA Medical Center, Department of Anesthesiology. Unexpected openings in faculty position at the rank of Assistant Professor. Desire recent graduate of anesthesiology fellowship with research training. Board eligible or certified. Active clinical services, research, and independent residency program in the department. Excellent southern Los Angeles location. Ample academic career opportunities with joint UCLA and LA County appointments. Competitive compensations. Send statement, CV, and list of references to Chingmuh Lee, MD, Professor and Chairman, Department of Anesthesiology, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509. Equal Opportunity Employer.

485I/K

VIRGINIA: CARDIOTHORACIC ANESTHESIOLOGIST

Immediate opening for BC/BE anesthesiologist, with cardiac fellowship training preferred, for a continually growing private adult cardiac anesthesia practice. Currently over 1300 pump cases per year, including EP studies and transplants. Send CV to Box 487I/K.

487I/K

ILLINOIS

Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for two campuses of the only hospital in the city since a recent merger. One facility will provide ophthalmology care; the second will provide ambulatory and in-hospital anesthesia services. No open heart or neurosurgery. Good opportunity with stable future. Please send CV to Box 488I/K.

488I/K

ANESTHESIOLOGIST

Board-certified or graduating resident to join three BC anesthesiologists. Fee for service. Private, NFP, 117-bed hospital. No craniotomies, OH. Near University of Notre Dame. Reply to Roberta Mann, Medical Staff Services, POB 880, Mishawaka, IN 46544. Telephone (219) 258-1346.

489I/K

ANESTHESIOLOGIST—EARLY PARTNERSHIP

POSITION AVAILABLE IMMEDIATELY: Full-time anesthesiologist, BC or BE, to fill available position immediately. One existing MDA and CRNAs seek individual to support expanding surgery service in progressive community hospital. Beautiful community located in the Great Smoky Mountains offers camping, white water rafting, fishing as well as one university and one community college. Send CV and three references to Mark Leonard, Administration, C.J. Harris Hospital, 59 Hospital Road, Sylva, NC 28779.

490I

Two full-time faculty positions at the Assistant/Associate/Full Professor level. The position requires abilities appropriate for a university position. Applicants must be board eligible and meet California license requirements. We have need for anesthesiologists trained in pain, OB, critical care, and pediatrics. Send curriculum vitae, bibliography, and names of three references to Gerald Gronert, MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. Position open until October 31, 1990. We are an Equal Opportunity/Affirmative Action Employer.

491IJ

CONNECTICUT

BC/BE anesthesiologist to join a four-physician group in a Litchfield County, 188-bed community hospital. Send CV to John Barrett, MD, 540 Litchfield Street, Torrington, CT 06790.

492IJ

REGIONAL ANESTHESIA/PAIN FELLOWSHIP

The Anesthesiology Department at Virginia Mason Medical Center is now accepting applications for the Moore/Bridenbaugh Fellow beginning in July 1991. This position includes a CA3 year in clinical anesthesia followed by a year of research fellowship in regional anesthesia. Contact Stephen M. Rupp, MD, Department of Anesthesia B2-AN, Virginia Mason Medical Center, P.O. Box 900, Seattle, WA 98111.

493I/K

CALIFORNIA, SAN FRANCISCO BAY AREA

Two BC/BE anesthesiologists needed immediately to join 18-MD group practice based in two hospital/two surgery center. Guaranteed six-figure salary to begin—then fee for service, early partnership available. Benefits included. Send CV to Box 494I.

494I

GEORGIA (SOUTH)

Close to Florida and Georgia beaches. Anesthesiologist BC or BE to join corporate group of MDs and CRNAs. First year salary, then partnership. No open heart, no neurosurgery, no routine OB. Full details first letter. Reply to Box 495I/K.

495I/K

ANESTHESIOLOGIST

BC/BE to join the medical staff of a small, rural community hospital. All types of anesthesia. Sport enthusiast's paradise, offering water skiing, fishing, and hunting. Send CV to Administrator, Abrom Kaplan Memorial Hospital, 1310 West 7th Street, Kaplan, LA 70548.

496I/L

FULL-TIME ANESTHESIOLOGIST

BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to 1415 18th Street, Lake Charles, LA 70601.

497I/B

OREGON
Obstetric Anesthesia Fellowship positions for subspecialty training in high-risk obstetrics. Opportunities for clinical and basic research. Send CV, three references, and a summary of career goals to Harvey Carp, MD, PhD, Director of Obstetric Anesthesia, Department of Anesthesiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201.

499I/K

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES
Excellent opportunity for an anesthesiologist who wishes to be director of a pain service in an academic department. Competitive stipend, good fringe benefits. Must be BC or BE and eligible for licensure in Arkansas. Send CV to Dr. E.F. "Bud" Klein, Jr, MD, Chairman, Department of Anesthesiology, University of Arkansas for Medical Sciences, Slot 515, 4301 West Markham, Little Rock, AR 72205. An Equal Opportunity Employer.

500IJ

ANESTHESIOLOGIST
Anesthesiologist—BC/BE, recently trained wanted to join busy practice—5 MDs, 9 CRNAs. No OH, no neonatology, little OB. Early partnership, excellent income, excellent benefits. Contact Anesthesia Associates, 302 North Marshall Avenue, Marshall, MI 49068.

501IJ

UNIVERSITY OF CALIFORNIA, DAVIS
One full-time position as an Assistant Professor of Clinical Anesthesiology. Must have a PhD and completion of at least 1 year postdoctoral fellowship. Training in neurobiology and physiological psychology required. Formal training in electrophysiology essential with three or more years experience in clinical electrophysiology. At least one additional year experience in operating room assessment with emphasis on auditory and somatosensory evoked responses and experience with assessment of EEG for carotid surgery. Some experience with olfactory evoked potentials or human olfactory testing desirable—as well as demonstrated history as research scientist, a consistent history of outside institutional funding, and demonstrated ability to write scholarly articles. California licensure as a psychologist or anesthesiologist. Send curriculum vitae, bibliography, and *names of five references* to Gerald Gronert, MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. Position open until October 31, 1990. We are an Equal Opportunity/Affirmative Action Employer.

502IJ

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Chief and/or Staff Anesthesiologist, BC/BE for 194-bed VA Medical Center, fully affiliated with Dartmouth-Hitchcock Medical Center and Dartmouth Medical School. Active teaching hospital. Academic appointment and salary commensurate with experience. Part-time position a possibility. Good schools, cultural offerings, beautiful country environment, good skiing, excellent bookstore. 2.5 hours from Boston, Massachusetts; 1.5 hours from Burlington, Vermont. For further information, call John M. Head, MD, Chief of Surgery, or Susanne Learmonth, Acting Chief of Anesthesia, 802/295-9363, extension 5290, or FTS 834-1290. Or send CV to above at VA Medical Center, White River Junction, VT 05001.

503I

ATTENTION CANADIAN ANESTHESIOLOGISTS ELIGIBLE TO WORK IN U.S. WITHIN NEXT SIX MONTHS
Large, profitable anesthesiology group in western New York state seeks several section directors as well staff anesthesiologists. This growing MD/CRNA group services modern 500-bed hospital affiliated with major university. Major center for head, neck, breast, and neuro surgery; no trauma or neonatal. Competitive salary, malpractice insurance, and relocation assistance, plus partnership option. All inquiries handled in strictest confidence. Send CV to Samantha Lloyd, CompHealth Anesthesia Search, 5901 Peachtree Dunwoody Road, #C-65, Atlanta, GA 30328. Or, for more information, contact Ms. Lloyd at 1-800-354-4050, toll-free.

509I

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383C/L

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498I

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504IJ

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473H/A

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Cancer Pain Management with a Controlled-Release Oral Morphine Preparation
Jeanne Lapin, Raymond W. Houde, Robert F. Kaiko, Nessa Coyle, Ada Rogers and Kathleen M. Foley

Celiac Plexus Block Following High-dose Opiates for Chronic Noncancer Pain in a Four-Year-Old Child
Darrell L. Tanelian and Michael J. Cousins

Clinical Observations on Controlled-Release Morphine in Cancer Pain
Vittorio Ventafridda, Luigi Saita, Lucilla Barletta, Alberto Sbanotto and Franco De Conno

Teaching Coping Strategies to Adolescents with Migraine (Part 4 of Special Series: Challenges in Pain Management)
Maureen A. Lascelles, S. June Cunningham, Patrick McGrath and Michael J.L. Sullivan

Effects of Biofeedback on Childbirth Pain
Pam Duchene

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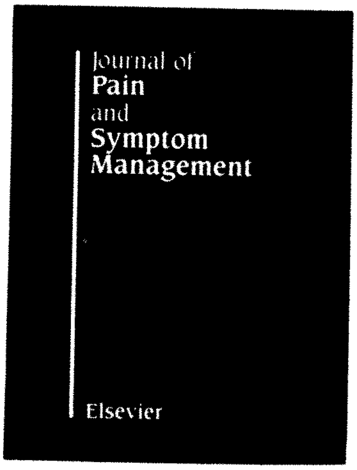

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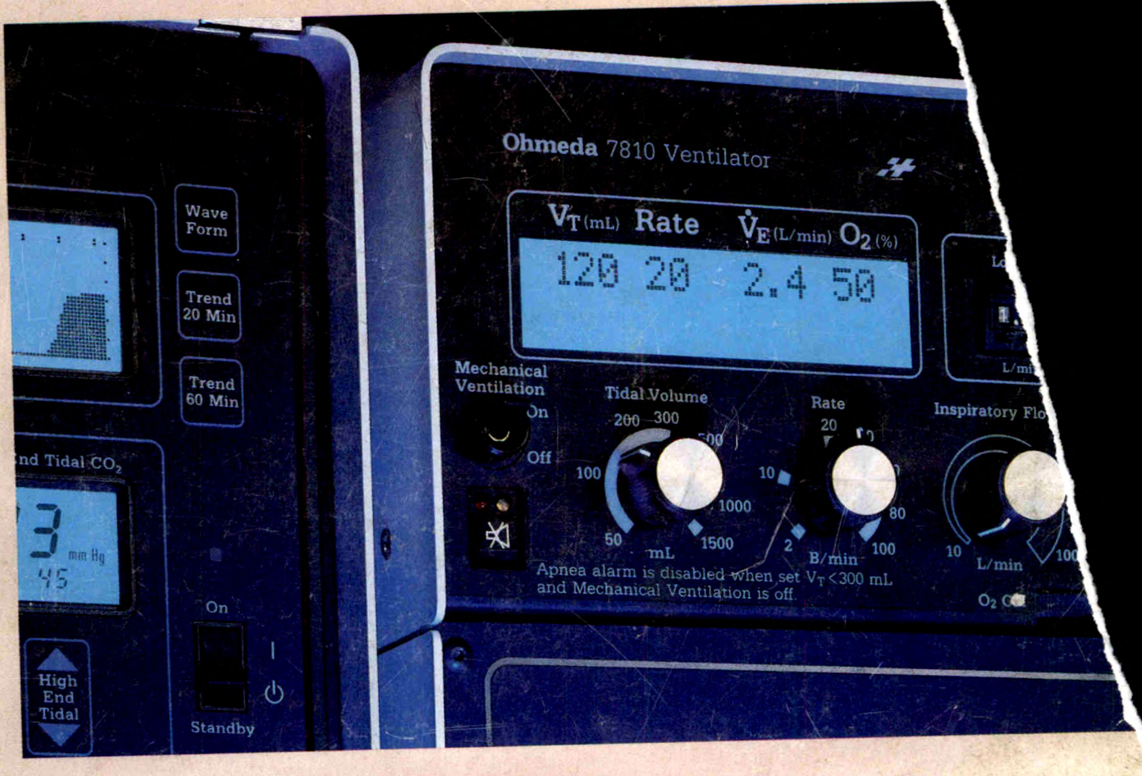

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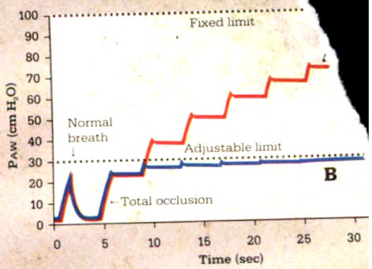

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